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Representation of faces in perirhinal cortex

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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by

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Abstract

The prevailing view of medial temporal lobe (MTL) functioning holds that its structures are dedicated to long-term declarative memory. Recent evidence challenges this view, suggesting that perirhinal cortex (PrC), which interfaces the MTL with the ventral visual pathway, supports highly integrated object representations that contribute to both recognition memory and perceptual discrimination. Here, I used functional magnetic resonance imaging to examine PrC activity, as well as its broader functional connectivity, during perceptual and mnemonic tasks involving faces, a stimulus class proposed to rely on integrated representations for discrimination. In Chapter 2, I revealed that PrC involvement was related to task demands that emphasized face individuation. Discrimination under these conditions is proposed to benefit from the uniqueness afforded by highly-integrated stimulus representations. Multivariate partial least squares analyses revealed that PrC, the fusiform face area (FFA), and the amygdala were part of a pattern of regions exhibiting preferential activity for tasks emphasizing stimulus individuation. In Chapter 3, I provided evidence of resting-state connectivity between face-selective aspects of PrC, the FFA, and amygdala. These findings point to a privileged functional relationship between these regions, consistent with task-related co-recruitment revealed in Chapter 2. In addition, the strength of resting-state connectivity was related to behavioral performance on a face discrimination task. These results suggest a mechanism by which PrC may participate in the representation of faces. In Chapter 4, I examined PrC connectivity during task contexts. I provided evidence that distinctions between tasks emphasizing recognition memory and perceptual discrimination demands are better reflected in the connectivity of PrC with other regions in the brain, rather than in the presence or absence of PrC activity. Further, this functional connectivity was related to behavioral performance for the memory task. Together, these findings indicate that mnemonic demands are not the sole arbiter of PrC involvement, counter to the prevailing view of MTL functioning. Instead, they highlight the importance of connectivity-based approaches in elucidating the contributions of PrC, and point to a role of PrC in the representation of faces in a manner that can support memory and perception, and that may apply to other object categories more broadly.

Keywords

Declarative Memory, Effective Connectivity, Face Discrimination, fMRI, Functional Connectivity, Medial Temporal Lobe, Perceptual Discrimination, Perirhinal Cortex, Resting-State Connectivity.

Co-Authorship Statement

All projects in my thesis were carried out under the supervision of my advisor, Dr. Stefan Köhler. Victoria Barkley collaborated on the study presented in Chapter 2, assisting with behavioral piloting. Chapter 3 benefited from theoretical guidance from Dr. R. Matthew Hutchison and statistical advice from Dr. Mark Daley. Statistical assistance for the data presented in Chapter 4 was provided by Drs. Jordan Poppenk and Andrea Protzner, who provided guidance with respect to the partial least squares analyses. Drs. Andrea Protzner and Cornelia McCormick provided advice on the structural equation modeling analyses. In addition, D. Adam McLean assisted with data analysis for the project presented in Chapter 4, and Dr. Anthony Cate contributed to the study design. All projects benefited from many helpful discussions with the members of Köhler lab. The written material in this thesis is largely my own work, but was also shaped by extensive feedback and input from my advisor, Dr. Stefan Köhler.

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List of Abbreviations and Symbols

Amy	Amygdala
ANOVA	Analysis of Variance
BOLD	Blood-Oxygen Level Dependent
D	Dimension
DMTS	Delayed Match-to-Sample
DNMTS	Delayed Non-Match-to-Sample
DLPFC	Dorsolateral Prefrontal Cortex
f	Frequency
FDR	False Discovery Rate
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GLM	General Linear Model
HR	Hemodynamic Response
LV	Latent Variable
mm	millimeter
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
ms	millisecond
MTL	Medial Temporal Lobe
MVPA	Multi-Voxel Pattern Analysis
OFA	Occipital Face Area
PFC	Prefrontal Cortex
PhC	Parahippocampal Cortex
PLS	Partial Least Squares
PPA	Parahippocampal Place Area
PrC	Perirhinal Cortex
ROI	Region of Interest
RT	Reaction Time
s	second
SEM	Structural Equation Modeling
STS	Superior Temporal Sulcus
T	Tesla
T1	Anatomical Magnetic Resonance Image
T2*	Functional Magnetic Resonance Image
TE	Echo Time
TR	Repetition Time
VLPFC	Ventrolateral Prefrontal Cortex
VVS	Ventral Visual Stream

Chapter 1

1 General Introduction

In classical psychological theory, memory and perception of visual objects have been viewed as reliant on distinct cognitive systems. Perception reflects the workings of an input system, whereas memory reflects the workings of a storage and retrieval system. A good deal of neuropsychological evidence supports this distinction as well. There are clear differences between cortical blindness and amnesia, for instance. This has led to the prominent view that memory and perception have distinct neural underpinnings (Squire and Zola-Morgan, 1991; Squire et al., 2004; Squire and Wixted, 2011). However, transformation of sensory experience into an enduring mnemonic representation requires interplay between input and storage systems. The interactive nature of this processing suggests that strong distinctions between memory and perception, with respect to neural correlates, might reflect an oversimplification of the true nature of neural representations in the brain. Indeed, recent evidence from functional neuroimaging and neuropsychology indicates that the distinction between memory and perception may not be as clear-cut as classically thought. Conditions can be instated experimentally that appear to recruit regions classically viewed as supporting object memory, even when memory demands are held to a minimum (Devlin and Price, 2007; Lee et al., 2006; Lee et al., 2005; O'Neil et al., 2009). Accounting for these findings may require a reconceptualization of the neural organization of memory and perception.

The overarching goal of my thesis is to probe the interface between recognition memory and visual perception of objects. In doing so, I will focus on the role of perirhinal cortex (PrC), a region located in the medial temporal lobe (MTL). This region has been classically viewed as a component of a MTL system dedicated to declarative memory functioning (Squire and Zola-Morgan, 1991; Squire et al., 2004; Squire and Wixted, 2011). However, recent findings suggest that PrC may also play a role in perceptual discrimination when stimuli are complex and highly similar, such that they cannot be distinguished based upon a single salient feature (Barense et al., 2007; Bussey et al., 2002; Bussey et al., 2003; Bussey et al., 2006; Lee et al., 2006; Lee et al., 2005;

Lee et al., 2008; O'Neil et al., 2009). Under these conditions, it has been suggested that PrC may be critical for the generation of highly integrated, object-level representations (Murray and Bussey, 1999). By 'representation,' I refer to the information content of neurons and populations of neurons that results from the transformation of sensory input into a neural code.

This representational view of MTL processing suggests that PrC contributions to object representation are critical when items share many features in common (sometimes referred to as conditions of high feature overlap or feature ambiguity). Under these conditions, discrimination between similar objects cannot rely on isolated representations of shared (i.e. non-diagnostic) features. Instead, features must be integrated into object-level representations that uniquely capture the relationships between object features to support discrimination. PrC is proposed to support these highly integrated object representations. The anatomical connectivity of PrC is of critical interest when examining the link between object memory and perception. Though it is located in a region of the brain classically viewed as dedicated to declarative memory, it receives extensive inputs from visual regions supporting object perception, interfacing these two systems (Suzuki and Amaral, 1994). This connectivity suggests that PrC may contribute to the representation of objects when earlier representations are insufficient for unique object representation, regardless of whether mnemonic or perceptual discrimination of stimuli is required.

The three projects that comprise my thesis were designed to probe the recently proposed role of PrC in object representations. In these projects, I used functional magnetic resonance imaging (fMRI) to examine PrC response in healthy human participants during discrimination of faces, based on perceptual or mnemonic task demands. Faces were selected as a stimulus class given my aim of maximizing feature overlap/ambiguity in order to address the predictions of the representational view. The highly regular feature configuration of faces (two eyes, above a nose, above a mouth) naturally gives rise to conditions of high feature overlap. Further, these stimuli were blended such that they were difficult to distinguish based on a single feature. By examining the task demands that recruit PrC, quantifying its intrinsic connectivity with

other brain regions during rest, and by examining the broader functional connectivity between PrC and the rest of the brain during recognition memory and perceptual discrimination tasks, the findings of my thesis expand recent work indicating that PrC is not limited to the support of long-term declarative memory tasks that require memory for facts and events. In Chapter 1, I first review the evidence that led to the emergence of the standard model of MTL functioning, i.e., that the role of this region is limited to declarative memory. I then highlight the critical role of PrC in object memory, before reviewing more recent findings that point to a new view of PrC functioning. According to this new view, PrC supports the representation of objects more generally, in a manner that can support both memory and perceptual discrimination.

1.1 Connectivity of the Medial Temporal Lobe

Cortical contributions to vision are shared amongst two major processing pathways in the brain (Goodale and Milner, 1992; Mishkin and Ungerleider, 1982). The dorsal visual pathway is responsible for the precise calculation of object metrics, allowing one to competently act on the world. The ventral visual pathway supports integration of visual information for the purpose of visual object identification. Response selectivity of ventral visual pathway neurons is thought to be hierarchically organized, with neurons in posterior regions typically exhibiting small receptive fields and selectivity for simple perceptual features (e.g., line orientations; Hubel and Wiesel, 1968), and cells in anterior regions exhibiting large receptive fields and selectivity for object-level representations (e.g., selectivity for specific face views; Freiwald and Tsao, 2010). However, the nature of information processing in the ventral visual stream is complex. The presence of feed-forward and feed-back projections indicate that information processing in the ventral visual pathway is interactive, progressing through a series of recurrent processing loops, rather than a simple linear progression (Kravitz et al., 2013).

Anterior aspects of the ventral visual pathway provide the major inputs to PrC. Perirhinal cortex, along with several other structures, including the hippocampus, parahippocampal cortex (PhC) and entorhinal cortex form the human MTL. The connectivity of these structures is arranged hierarchically, with the perirhinal and parahippocampal cortices providing the main inputs to the entorhinal cortex, which in

turn, provides inputs to the hippocampus (Suzuki and Amaral, 1994). Examination of the macaque brain has revealed that well over half of the inputs to PrC come from areas TE and TEO, inferotemporal cortex regions recognized as critical for object perception (Suzuki and Amaral, 1994). Classically, TE is viewed as the most anterior extent of the ventral visual object-processing pathway (Ungerleider and Mishkin, 1982). Extensive connectivity between TE and PrC suggests that PrC may perform an additional level of processing on the representational content of TE neurons in support of object memory and recognition (Murray and Bussey, 1999; Suzuki and Amaral, 1994). Conversely, PhC receives extensive inputs from dorsal visual pathway regions such as retrosplenial and posterior parietal cortices (Suzuki and Amaral, 1994). In addition, PhC receives inputs from the ventral visual pathway, in particular V4. Entorhinal inputs are segregated with respect to PrC and PhC connectivity (Schultz et al., 2012; Suzuki and Amaral, 1994). PrC projects to the lateral entorhinal cortex, while PhC projects to medial entorhinal cortex. PhC also sends significant projections to PrC, indicating some level of interaction (though largely unidirectional) between these cortices before information reaches entorhinal cortex. While the sources of inputs to PrC are primarily visual (Suzuki and Amaral, 1994), it receives inputs from all sensory modalities, and is recognized as an important hub region supporting multimodal integration (Holdstock et al., 2009; Tyler et al., 2013; Tyler et al., 2004).

1.2 The Standard View of MTL Functioning

In 1953, Henry Molaison (known as HM in the scientific literature) underwent experimental surgery for the treatment of intractable epilepsy. The surgery, performed by William Scoville, involved the bilateral resection of the MTLs. Subsequent assessment of the lesion extent using magnetic resonance imaging (MRI) revealed that the surgery removed most of the amygdala complex and entorhinal cortex, as well as the hippocampus, sparing the posterior two centimeters of this structure (Corkin et al., 1997). While the surgery relieved HM's seizures, it was not without consequence; he acquired dense anterograde amnesia, leaving him unable to acquire new episodic memories, that is, memories that are linked to specific times and places (Scoville and Milner, 1957). He also had difficulty learning new facts and vocabulary, indicating a problem with semantic

memory (O'Kane et al., 2004). Episodic and semantic memory fall under the umbrella of declarative memory, a term used to describe memory for content that can be consciously recalled after delays that extend beyond a few seconds and when continuous rehearsal is prevented (Squire and Zola-Morgan, 1991). Critically, HM's other mental faculties were preserved, including visual perception as assessed using standard neuropsychological tests of visual acuity available at the time (Milner, 1972). Seminal work by Canadian psychologist Brenda Milner revealed that HM could exhibit new learning on non-declarative memory tasks, such as the procedural mirror-tracing task (Milner, 1962). The combination of the precise and quantifiable nature of the brain damage, given its surgical origin, as well its profound and apparently selective mnemonic consequences, provided powerful evidence that the integrity of the MTL is critical to declarative memory functioning in humans.

The discovery of a relationship between the MTLs and declarative memory functioning encouraged researchers to probe the contributions of MTL structures to declarative memory in a more targeted manner. Initial attempts to create an animal model of amnesia for this purpose failed due to a lack of understanding that monkeys and humans can complete memory tasks using different strategies (Squire, 2009). It is common to provide a monkey with extensive training on a task, and it took many years to appreciate that this training can invoke a basal ganglia-based habit learning system, which is resistant to hippocampal damage. Moreover, the development of an animal model of declarative memory was not a trivial task; experimental assessment of consciously retrieved memories is generally facilitated by verbal report of the contents of a memory, which is not feasible in the monkey. Tasks also needed to include the three components of declarative memory: encoding, maintenance over a delay, and retrieval. These constraints led to the wide adoption of the delayed non-match-to-sample (DNMTS) task for the assessment of memory in non-human primates (Mishkin, 1978). In this task, an object is first presented to the animal. Following a delay period, a pair of items is presented and the animal is required to choose the novel item. Critically, the task uses a choice phase rather than verbal report to provide a quantifiable measure of declarative-like memory in non-human primates. There is also an alternate version of this

task, the delayed match-to-sample (DMTS) task, which requires selection of the studied item during the choice phase.

Initial attempts in animal models to isolate the specific locus of object memory were unsuccessful. Instead, deficits were revealed in animals following combined lesions to the hippocampus and amygdala, both of which were included in the MTL resection of patient HM (Mishkin, 1978). These deficits were delay-dependent, indicating that impairments were related to maintenance and retrieval demands, rather than the perception of the sample stimulus. This pattern reflected an important aspect of the impairments in amnesics; short lists of numbers or words can be successfully maintained over brief delays, suggesting intact working memory and visual perception, but cannot be maintained over longer delays (Drachman and Arbit, 1966; Sidman et al., 1968). Notably, animals with more circumscribed lesions to the hippocampus exhibited less severe declarative memory deficits than those with lesions that extended beyond the hippocampus into other MTL structures (Zola-Morgan et al., 1994). In other words, rather than reflecting damage to any one structure in particular, deficits in declarative memory appeared correlated with the overall extent of damage to the structures comprising the MTL. This led to an influential and predominant view of MTL functioning; MTL regions work in concert to support declarative memory as an integrated system (Squire and Zola-Morgan, 1991; Squire et al., 2004; Zola-Morgan et al., 1994). This view acknowledges some potential specialization of MTL structures as related to their distinct anatomical inputs, but does not support specialization of MTL structures with respect to underlying processes (i.e., distinctions between regions that contribute to feelings of familiarity and those supporting recollection), nor does this view support non-mnemonic roles of MTL structures, such as a role in visual perception.

1.3 Evidence for Specialization of MTL Structures

The view that combined damage to the hippocampus and amygdala was necessary to produce declarative memory deficits fell out of favor when exceptions were demonstrated. Lesions to either the hippocampus or the amygdala were found to cause impairments in DNMS tasks when the cortex underlying these regions (entorhinal, perirhinal, and parahippocampal) was also damaged. (Murray and Mishkin,1986; Zola-

Morgan and Squire, 1986). Damage to this underlying cortex was a by-product of the surgical approach used to create the hippocampal-amygdala lesions, leaving open the possibility that damage to the MTL cortex, and not the combined amygdala-hippocampal lesion, was responsible for deficits in object memory. In fact, an initial study addressing this issue revealed object memory deficits following deactivation (by cooling) of the inferior temporal gyrus of the macaque (Horel et al., 1987), which also included PrC. Further surgical explorations uncovered deficits following combined removal of perirhinal and parahippocampal cortices (Zola-Morgan et al., 1989), or perirhinal and entorhinal cortices (Eacott et al., 1994; Gaffan and Murray, 1992; Meunier et al., 1993), indicating that MTL cortex, rather than the hippocampus and amygdala, was critical to object memory. Meunier et al. (1993) demonstrated that recognition deficits following selective PrC lesions were comparable to those following combined entorhinal/perirhinal lesions, with selective entorhinal lesions having little effect on a DNMTS task. Additionally, animals with selective pharmacological lesioning of the amygdala and hippocampus demonstrated intact object recognition memory for delays as long as 40 minutes, highlighting the critical impact of damage to the underlying cortex, rather than damage to the hippocampus and amygdala, on object recognition memory (Murray and Mishkin, 1998). Together, these studies point to an important role of PrC in object recognition memory. Further, they highlight potential functional specializations of MTL structures that may permit these regions to make unique contributions to declarative memory functioning, contrary to the standard model of MTL functioning.

The notion that distinct MTL structures may have differing contributions to memory has been a major focus of memory research over the past twenty years, leading to the emergence of a new model of MTL contributions to declarative memory functioning. This new view draws a distinction between recollection, i.e., the retrieval of a declarative memory accompanied by contextual information, and familiarity, i.e. the retrieval of declarative memory in the absence of contextual information. Critically, it has been proposed that there is an anatomical distinction between regions that support these two processes, with the hippocampus supporting recollection, and PrC supporting familiarity (Aggleton and Brown, 1999). This proposal is controversial, as distinctions between recollection and familiarity can be recast in terms of memory strength. It may be the case

that increased hippocampal involvement associated with recollection of episodic details reflects greater recruitment of MTL structures for strong memories (memories associated with high confidence, and/or where many details of the encoding event can be retrieved) as compared to weak memories (memories associated with low confidence and/or where few details of the encoding event can be retrieved). The parsimony of a single process strength-based account has caused some to question whether a distinction between recognition and familiarity is worthwhile for understanding MTL contributions to declarative memory functioning (Squire et al., 2007; Wixted and Squire, 2010). Support for such a distinction, however, comes from patients with selective hippocampal lesions who exhibit intact item familiarity in the absence of episodic memory (Aggleton et al., 2005; Mayes et al., 2004; Yonelinas et al., 2002). Further, the opposite pattern of findings, i.e., impaired familiarity and intact recollection, has been observed in a patient following an anterior temporal lobe resection that impacted PrC but preserved the hippocampus (Bowles et al., 2007). These findings point to dissociable roles of hippocampus and PrC with respect to recollection and familiarity processes, consistent with the proposal by Aggleton and Brown (1999). Some neuroimaging findings also support this distinction. For example, hippocampal blood-oxygenation-level-dependent (BOLD) response during encoding is often elevated for items retrieved with associated contextual details about the study episode, whereas PrC response is elevated during encoding of items subsequently recalled in the absence of additional contextual information (for review, see Diana et al., 2007).

A related proposal for the roles of PrC and the hippocampus suggests that PrC supports the representation of item information, while the hippocampus supports relational memory, that is, the encoding of the relationships between items and their context (Eichenbaum, 2004). A similar account proposes that PhC supports the encoding and retrieval of context information, while PrC supports the encoding and retrieval of item information. The role of the hippocampus in this model is to bind item and context information together to support episodic memory (Diana et al., 2007). Each of these models point to a role of PrC in object/item memory, and a role of the hippocampus in the binding of objects and context into episodic memories. Such a view is consistent with connectivity between PrC and the ventral visual pathway, and the evidence reviewed

above indicating that PrC is critical for visual object memory.

1.4 Contributions of PrC to Cognitive Functioning Beyond Declarative Memory

The studies reviewed above provide strong evidence for a role of PrC in object recognition memory. However, Eacott et al. (1994) challenged the view that impairments following PrC lesions are exclusively mnemonic in nature. Consistent with the findings presented above, comparison of match-to-sample performance of rhinal cortex-lesioned macaques and controls revealed delay-dependent deficits. Eacott and colleagues next minimized the mnemonic demands of the task by removing the delay period. Notably, the deficit persisted, despite equivalent pre-operative performance of controls and PrC-lesioned animals. Critically, this deficit was revealed using a trial-unique set of stimuli. This finding suggests that impairments may reflect the representational demands associated with trial unique stimuli, rather than the mnemonic demands associated with the delay. To further examine the consequences of representational demands on match-to-sample performance, the stimulus set was reduced to two items. In this scenario, the choice phase always consisted of the same two stimuli, one of which was designated as the target in the sample phase. Under these conditions, PrC-lesioned macaques performed similarly to control animals, even when the delay was re-instated. Importantly, these findings provide insight into the specific task demands that rely on PrC. Lesions impacted performance on tasks that employed difficult to discriminate, trial-unique stimuli, not performance on familiar or small stimulus sets, even when a delay period was imposed. Thus, the role of PrC appears better captured by the representational rather than mnemonic demands of discrimination tasks.

1.5 Perceptual Deficits Following MTL Damage in Non-Human Primates

To achieve successful performance on a typical visual discrimination task, the animal must possess some knowledge of what item is designated correct. Correct items are typically designated by training animals to associate certain items with a reward. For instance, a great deal of early work examining the role of the PrC (both in humans and

monkeys) used the concurrent discrimination learning task (e.g., Barense et al., 2005; Barense et al., 2010; Buckley and Gaffan, 1997; Buckley and Gaffan, 1998; Bussey et al., 2003; Saksida et al., 2006; Saksida et al., 2007). In this task, the subject must learn reward contingencies associated with a set of items. A pair of items drawn from the set is presented on each trial, one item designated correct, the other incorrect. The subject must learn, by trial and error, the reward contingencies for the set. The set of stimulus pairs is repeated until the subject can reach a certain performance level (measured using trials to criterion). A simple example would be a stimulus set composed of red squares and blue circles, where the former, but not the latter, is always rewarded. Performance in this case can be supported by attention to a single feature, color or shape, as both are diagnostic with respect to reward status. Sets can also be constructed such that accurate performance requires a 'conjunctive' rule. For instance, introducing unrewarded blue squares and red circles now requires the subject to integrate both color and shape information to learn the problem set to criterion, as neither feature alone is sufficient for identification (i.e., individual features are ambiguous). Compared to controls, patients and monkeys with PrC damage perform normally when single features are a reliable indicator of the correct item, such as if red items are always designated correct and blue items incorrect. However, PrC lesions have a significant impact when discrimination relies on the integration of features (the representation of feature conjunctions; e.g., Barense et al., 2005; Bussey et al., 2003). While the concurrent discrimination learning task has shed light on the role of PrC in processing the conjunctive relationships of features, as task performance relies on memory for the correct item, this approach presents a major challenge when attempting to tease apart the mnemonic and perceptual contributions of PrC.

Ideally, to avoid confounds with declarative or other memory processes, the subject should be able to deduce the 'correct' choice without pre-training on a stimulus set. The oddity (or oddball) task meets this condition, and is thus ideally suited for assessing perceptual discrimination ability, while minimizing the contributions of declarative memory to task performance. In this task, stimulus arrays are presented, constructed such that one of the items (the target) in the array is perceptually dissimilar from the others. The subject must select the 'odd item out'. The strength of this task, from an

experimental standpoint, is that once the subject acquires the rule (i.e., choose the odd stimulus out), the nature of the stimulus array, rather than memory for a particular studied item, guides identification of the target. In addition, once the rule has been acquired, the subject can be tested with a variety of stimulus types. Examining perceptual discrimination performance in macaques, Buckley and Gaffan (2001) revealed that PrC lesions differentially impacted performance on a variety of oddity tasks. Monkeys exhibited performance similar to controls on tasks that examined oddity discriminations of shape, size, and color, even when discriminations were made quite challenging. Thus, PrC lesions did not impact discrimination performance when the oddball could be determined based upon a simple perceptual feature. When animals were tested on discrimination problems that could not be resolved based on a single perceptual feature (those requiring generalization across viewpoints to identify the oddball, for example), PrC-lesioned animals were impaired. Intact performance on a subset of tasks indicates that PrC-lesioned animals were able to maintain the 'choose the odd one out' rule following PrC removal. These findings were influential because they suggested that PrC damage impairs performance when discrimination tasks require highly integrated stimulus representations (i.e., when items cannot be differentiated based upon simple features such as size, shape or color),

1.6 The Representational Account of MTL Functioning

Evidence indicating that PrC processing is critical to accuracy on discrimination tasks that lack a long-term declarative memory component contradicts the standard view of MTL functioning. To account for these early key findings of deficits across different discrimination tasks, and others that were reported subsequently, a new representational view of MTL functioning was proposed in the late 1990s by Murray, Bussey and colleagues (Bussey and Saksida, 2007; Graham et al., 2010; Murray and Bussey, 1999). This view, which was also guided by the anatomical connectivity between PrC and regions in the ventral visual pathway, reconceptualizes PrC as an extension of the ventral visual processing pathway, rather than as a structure that is dedicated to declarative memory. Specifically, PrC is proposed to contribute to the generation of highly integrated object representations that can support fine-grained discrimination between objects that

are highly similar, and therefore not easily discriminable based upon a single feature.

How could a PrC-based representation support both the perceptual discrimination of stimuli with high feature overlap, as well as the maintenance of object representations over a delay? Recent computational modeling work indicates that these two apparently distinct functions can be reconciled by appealing to a role of PrC in the coding of object features into integrated, object-level representations. In these models (Bussey and Saksida, 2002; Cowell et al., 2006; Cowell et al., 2010), when discriminating between highly similar items, such as a pair of similar faces, feature representations common to the objects become active. These feature representations, while sufficient for distinguishing the pair when the presence or absence of a single visual feature is diagnostic, do not permit discrimination of objects with many shared features, i.e. with considerable feature overlap. By representing the unique combination of features that comprise an object, highly integrated representations at the level of PrC can serve to resolve feature ambiguity (and interference) by specifying not only the co-occurrence of features that define an object, but also their unique configuration. In other words, these conjunctive feature representations support the discrimination of complex stimuli with overlapping visual features when no individual feature supports discrimination. It is important to note that conjunctive feature representations are proposed to be represented throughout the VVS, but the level of feature integration increases as information progresses anteriorly along the VVS, whereby PrC supports the conjunctive representations of features integrated at the object level.

Following the computational account just reviewed, the unique representation of objects aids in perceptual discrimination. However, it also confers an additional benefit: integrated object representations can be better maintained over a delay. Ongoing perceptual experience, including exposure to irrelevant items between study and test, results in the activation of a wide variety of feature representations, some of which may be common with the object being maintained. This results in interference in the network, inducing a form of forgetting. The unique conjunctions of features, proposed to be supported by PrC, are less likely to be encountered during the delay period. Thus, the highly integrated nature of PrC-based representations affords resistance to interference,

supporting object memory. In the absence of highly integrated object-level representations, less integrated conjunctions of features must be relied upon for discrimination, representations which are vulnerable to interference from visual experience during a delay (Cowell et al., 2006; Cowell et al., 2010).

The computational role of PrC just described accounts for the selective pattern of discrimination deficits reported by Buckley et al. (2001), in which PrC-lesioned macaques were unimpaired on oddity discrimination tasks that could be resolved based upon simple features such as size, shape, or luminance. However, these animals were impaired when stimuli could not be discriminated based upon simple features. This model also accounts for delay-dependent deficits in item recognition following PrC lesions – longer delays increase the vulnerability of a maintained item to interference from features encountered during these delays. In addition, intact memory performance on DMTS tasks following PrC resection are predicted by this view when set size is limited, consistent with the findings of Eacott et al. (1994).

1.7 The Representational Account: Patient Evidence

Human patient research provides convergent evidence for a role of PrC in perceptual discrimination tasks involving stimuli (including faces) with highly overlapping or ambiguous features. Selective perirhinal lesions are rare in humans; however insight into the contributions of PrC can be gleaned by comparing discrimination performance of patients with selective hippocampal lesions to those with broader MTL damage that includes PrC.

Lee et al. (2005) examined the performance of patients with selective hippocampal damage, patients with broader MTL damage that included PrC, and their respective age-matched controls using a simultaneous match-to-sample task. This task required subjects to determine which of two morphed (blended) images was most similar to a simultaneously presented sample image. Patients with hippocampal damage exhibited deficits limited to the discrimination of scenes, whereas MTL patients were impaired at discriminations of scenes, faces, and objects as compared to controls. Deficits in scene discrimination are anticipated following hippocampal damage, which was common to

both patient groups. However, the selective nature of object and face discrimination deficits point to a role of MTL cortex, in particular PrC, in support of these tasks. Consistent with a representational view, both groups performed as well as controls when discriminating colors and abstract art that could be resolved based on a simple perceptual feature.

In addition to simultaneous match-to-sample tasks, in which the target is viewed below the sample, impairments on discrimination tasks following MTL damage have also been demonstrated using oddity tasks involving face and scene stimuli, in which the target could be any image in the array (Lee et al., 2005). These effects hint at a division of labor between PrC and the hippocampus with respect to object (including faces) and scene processing. More formal assessment of this division of labor comes from a comparison of patient groups with more significant hippocampal atrophy (Alzheimer's patients) and a group with more significant damage to PrC (semantic dementia patients; Lee et al., 2006). These patient groups revealed distinct impairments on oddity tasks involving faces and scenes. In line with a representational view of MTL functioning, Alzheimer's patients were selectively impaired on the scene oddity task, in contrast to semantic dementia patients who exhibited selective impairment on the face oddity task. Importantly, deficits in object discrimination following PrC lesions have been linked to representational demands. Focusing on object oddity discriminations, Barense et al. (2007) revealed impairments in patients with MTL damage (that included PrC) for oddity judgments of real and artificially created objects. Further, the extent of the deficit was related to the item discriminability, that is, the extent to which the oddball shared features with the non-target items. Again, oddity judgments that were comparably difficult but could be resolved based upon simple feature characteristics such as size or color were not impaired.

Despite multiple studies indicating discrimination deficits following MTL damage, conflicting findings have also been reported, generating a good deal of controversy with respect to PrC contributions to visual perception. Employing a task design similar to Lee et al. (2006), and examining patients with an arguably better quantified lesion extent, Shrager et al. (2006), failed to reveal perceptual deficits in patients with MTL damage.

Similarly, Levy et al. (2005) assessed discrimination performance for morphed images and failed to reveal a deficit in two patients with PrC damage as compared to controls. These findings support the standard model of MTL functioning, and call into question the notion that PrC supports discrimination of objects that possess highly similar and overlapping features.

To account for these discrepant findings, some have proposed that MTL patients who exhibit deficits on visual discrimination tasks may possess damage that extends into adjacent regions of inferolateral temporal cortex, regions more classically associated with visual perception (Kim et al., 2011; Shrager et al., 2006; Suzuki, 2009). Assessment of structural MRI images cannot definitively rule out this possibility, as disconnection of white matter tracts are not easily detected in these images. However, convergent evidence of PrC contributions to the representation of objects comes from several functional neuroimaging studies in healthy individuals.

1.8 The Representational Account: Functional Imaging Evidence

Functional neuroimaging of PrC using fMRI presents certain challenges, due to the proximity of the region to the air-tissue interfaces of the sinuses. Magnetic suceptibility artifacts can cause both signal dropout and distortion in this region, requiring special consideration with respect to the slice aquisition and scanning protocol. Initial neuroimaging evidence in support of the representational view came from a different imaging modality, positron emisison tomography. While this approach is more invasive than fMRI, as it requires injection of radioactive tracers into the subject, it does not suffer from issues related to magnetic susceptibility artifacts. Comparing PrC activity during simple and more difficult object and feature discrimination tasks, Devlin and Price (2007) revealed greater PrC involvement in object oddity tasks that required viewpoint invariant representations as compared to feature oddity tasks that could be resolved based on color or simple shape. Detection of the oddball in an array in which the target and foils are presented from different viewpoints emphasizes reliance on a viewpoint invariant representation over a feature-based discrimination strategy because viewpoint changes occlude image features. With improvements in MRI hardware and sequences, the

functional role of PrC has been increasingly assessed using fMRI. A more recent study by Barense et al. (2010) used fMRI to compare PrC activation during oddity discriminations for faces, objects, and scenes. Difficult trials required judgements of stimulus arrays in which item viewpoint varied. Easy trials required judgements of object arrays presented from the same viewpoint, in which two of the three images were identical. In this easy condition, the target could be identified based on overall differences in item shape or contrast. Comparison of BOLD response in viewpoint-variant and viewpoint-constant conditions, within each stimulus class, revealed increased PrC involvement for objects and faces.

Evidence from fMRI also supports differential contributions of PrC and the hippocampus to object and scene discrimination, as suggested by the comparison of Alzheimers and semantic dementia patients (Lee et al., 2006). During oddity discriminations of faces, PrC exhibited heightened activity (Lee et al., 2008). In contrast, the response of the posterior hippocampus exhibited heightened response during scene oddity judgments. This pattern is consistent with the neuropsychological evidence for a double dissociation between the hippocampus and PrC in the discrimination of scenes and faces respectively (Lee et al., 2006)

While several fMRI studies examining the role of PrC in perceptual oddity tasks have relied on viewpoint manipulations to increase reliance on PrC-based representations, other stimulus manipulations can also increase PrC involvement in discrimination tasks. Image morphing, a procedure that blends images together such that they share many features in common, has also been used successfully to examine PrC contributions to object representation (O'Neil et al., 2009; Saksida et al., 2006). My Masters's thesis research (O'Neil et al., 2009) examined PrC response during discrmination of stimulus arrays composed of morphed faces, directly comparing PrC activity under conditions of high and low mnemonic demands. A memory task required the discrimination of the studied face from two very similar foils following a delay, whereas a perceptual discrimination task required selection of the odd item from the stimulus triplet display. If the standard view of MTL functioning is correct, then declarative memory demands should determine PrC involvement. Instead, both tasks

were found to activate PrC similarly as compared to a control task that could be solved based upon a simple perceptual feature (a luminance discrimination task). Thus, it appears that PrC is not recruited based upon memory demands alone. I also manipulated task difficulty in both memory and oddity tasks. In the memory task, this was achieved by manipulating the number of times images were studied, while in the oddity task the discriminability of the oddball stimuli was manipulated in order to make it more or less similar to the foil stimuli. While PrC activity was modulated by accuracy in both memory and oddity discriminations, it was not modulated by the difficulty manipulation. Activity in a region more classically linked to face processing, the fusiform face area (FFA), reflected accuracy only in the easy oddity condition, consistent with a more limited representational capacity of this earlier ventral visual pathway region.

1.9 Benefits of Using Faces to Examine the Representational Account

Given the theoretical importance of achieving a high degree of object feature overlap in order to probe the representational role of PrC, several studies have included faces as a stimulus class (Barense et al., 2007; Barense et al., 2010; Barense et al., 2011; Lee et al., 2005; Lee et al., 2006; Lee et al., 2008; Mundy et al., 2012; Mundy et al., 2013; O'Neil et al., 2009). Faces naturally share high feature overlap due to their common first-order configuration (two eyes, above a nose, above a mouth; Maurer et al., 2002). As a result of this regular feature arrangement, individuation of faces relies to a large extent on the integration of features and their spatial relationships. Indeed, humans are sensitive to changes in feature spacing so small they approach the limits of visual acuity (Haig, 1984). A further benefit to using faces to probe the representational nature of PrC relates to the fact that regions supporting face processing have been the focus of extensive research. As a result, comparison of PrC and upstream ventral visual pathway regions to elucidate the representational contributions of PrC is relatively straightforward, given the well-established and reliable approaches developed to identify face-selective regions such as the FFA.

Face perception in humans is supported by several regions identified as exhibiting preferential, but not exclusive responses to faces as compared to other stimulus classes.

This system has been extensively researched in patients, typically functioning individuals, and in monkeys. Consequently, this research has generated a huge literature, and I provide only a basic summary of core findings with respect to the neural organization of the face processing network. The FFA, the most studied of the regions, exhibits sensitivity to facial identity and manipulations of feature relationships (Kanwisher et al., 1997; Kanwisher and Yovel, 2006). The posterior region of the superior temporal sulcus (STS) has been shown to support representation of more dynamic aspects of faces, related to expression as well as eye movements (Hoffman and Haxby, 2000; Kesler-West et al., 2001; Narumoto et al., 2001; Streit et al., 1999; Winston et al., 2004). In addition, the occipital face area (OFA) is sensitive to isolated feature manipulations (Pitcher et al., 2011; Puce et al., 1996). Together, these regions have been referred to as forming the 'core' face processing network (Gobbini and Haxby, 2007; Haxby et al., 2000; Haxby et al., 2002). Though face perception has been extensively studied using fMRI, researchers have largely embraced a tradition of targeted probing of 'the big three' regions (FFA, OFA, and STS), following their identification using functional localizer scans. While extremely informative, a consequence of this approach is that face selectivity of regions outside of targeted regions of interest can remain unreported.

While PrC as a whole is critical for the representation of objects more generally (e.g., Barense et al., 2010; Litman et al., 2009), several reports that have emerged over the past five years indicate that aspects of PrC may exhibit some specialization for face processing. Examination of the face processing network in the macaque has revealed a ventral aspect of the anterior temporal lobe (Freiwald and Tsao, 2010; Moeller et al., 2008; Mur et al., 2010; Pinsk et al., 2009; Rajimehr et al., 2009; Tsao et al., 2003; Tsao et al., 2008). Targeted assessment of face selectivity in humans has revealed a functionally homologous region in the vicinity of PrC (Nasr and Tootell, 2012; Rajimehr et al., 2009; Rossion et al., 2012; Tsao et al., 2008; Von Der Heide et al., 2013). Face selectivity has been demonstrated using a variety of tasks, including 1-back identity tasks (Mundy et al., 2012; Nasr and Tootell, 2012; Rossion et al., 2012), gender discrimination, as well as under more passive viewing conditions (Mundy et al., 2012; Rajimehr et al., 2009). These studies report face selective cortex centered in the anterior extent of the collateral sulcus

(see Nasr and Tootell, 2012 supplemental material for subject-level localization), a reliable anatomical indicator of PrC (Insausti et al., 1998)

What contribution does the anterior temporal lobe make to face processing? Some evidence comes from congenital prosopagnosics, individuals with a lifelong impairment in face recognition. Structural and functional connectivity analyses of the inferior longitudinal fasciculus, which connects FFA, OFA, and the anterior temporal lobe, have revealed distinctions between congenital prosopagnosics and typically functioning individuals. Congenital prosopagnosics exhibit reduced white matter integrity of this pathway and the extent of reduction is correlated with behavioral face recognition performance (Thomas et al., 2009). With respect to the specific contributions of PrC to the representation of faces, evidence in macaques has revealed identity-based face selectivity in anterior face patch neurons (Freiwald and Tsao, 2010). This identity-based response is not common to more posterior face patches, suggesting integration of visual information in this region results in identity-based selectivity. In the human, the specific contribution of PrC to face processing is an open question. Nestor et al. (2011) revealed a region in the vicinity of PrC that, in conjunction with aspects of fusiform gyrus, supported individuation of faces. The distribution of voxels that contained identity information was evenly distributed across these regions, highlighting the possibility that identity information in the human face processing network may be distributed.

Together, these findings indicate an important role of PrC in discriminating face stimuli, consistent with a role of PrC in discriminating stimuli with highly overlapping or ambiguous features.

1.10 Goals of Current Studies

The results of my Master's thesis provided a starting point for the research program presented here. In particular, demonstration of comparable PrC response in memory and perceptual discimination tasks is consistent with the view that mnemonic demands are not the sole arbiter of PrC involvement in a task. Motivated by this evidence, the studies that comprise my PhD thesis aim to further examine predictions of the representational view in order to probe the functional role of PrC in both memory and perception. In each of the

three core chapters of my thesis, I address each of the following questions with a separate fMRI study:

1) Is PrC involvement in perceptual tasks purely stimulus driven, or does PrC involvement in perceptual discrimination tasks hinge on task requirements related to the development of highly integrated and distinct object representations for individuation?

In Chapter 2, I present a new fMRI study that addresses the link between representational demands and PrC involvement in visual discrimination tasks. If PrC is recruited by the representational demands of a task, then manipulation of the extent to which stimuli must be uniquely represented should be reflected in PrC activity. To assess this hypothesis, I manipulated the extent to which task demands emphasized the individuation of faces, while holding stimulus complexity constant. In addition, I examined the effects of a face inversion manipulation on PrC processing. Face inversion is thought to impact the extent to which configural processing of features can be brought to bear on face perception, reducing the extent to which faces can be processed in holistic manner (see Rossion, 2008 for review). To anticipate my findings, PrC was impacted by the extent to which task demands required individuation of faces, consistent with the predictions of the representational view. The effects of inversion were less clear-cut, a point that I return to in the chapter.

2) Is face-selective activity in PrC related to intrinsic functional connectivity between PrC and the rest of the face-processing network?

In Chapter 3, I examine the extent to which face-selective aspects of PrC may be intrinsically connected to other regions within the face processing network, even in the absence of task or stimulus processing demands. To address this issue, I examined resting-state fMRI data, collected in conjunction with functional localizer scans that permitted identification of the face processing network in each subject. In addition, behavioral measures of face recognition were collected in the same subjects, allowing the behavioral consequences of resting-state connectivity to be probed. Given the non-human primate, human patient, and imaging studies reviewed above that point to PrC involvement in the discrimination of faces, I predicted that PrC contributions to face

perception would reflect some degree of integration of this region within the face processing network, as measured using resting-state fMRI. To anticipate my findings, PrC and FFA were found to exhibit functional connectivity during rest that was not common to other regions in the face processing network. Further, this connectivity was found to be behaviorally relevant.

3) Are PrC-based representations differentially recruited in the context of memory and perceptual discrimination tasks?

Common involvement of PrC in recognition memory and perceptual discrimination tasks is consistent with a representational view, but this finding begs the question of how these common PrC-based representations are differentially recruited in the support of distinct task demands. In Chapter 4, I re-examine my Master's thesis data with a focus on the functional and effective connectivity of PrC during recognition memory and visual oddity tasks. The standard view of MTL functioning predicts differential involvement of PrC in these tasks, given their distinct declarative memory demands. A representational account of PrC functioning predicts common involvement in recognition memory and perceptual discrimination tasks, given my selection of morphed faces as stimuli, which were carefully designed to have highly overlapping visual features. Moreover, if PrC supports item representations, differential task demands associated with recognition memory and visual oddity tasks should be reflected in differential connectivity between PrC and the rest of the brain. To anticipate, my findings revealed that PrC exhibits both common and distinct patterns of functional connectivity with the rest of the brain during recognition memory and perceptual discrimination tasks.

1.11 References

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *The Journal of Behavioral and Brain Sciences, 22*, 425-444.

Aggleton, J. P., Vann, S. D., Denby, C., Dix, S., Mayes, A. R., Roberts, N., & Yonelinas, A. P. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia*, *43*, 1810-1823. doi: /j.neuropsychologia.2005.01.019

Barense, M. D., Bussey, T. J., Lee, A. C. H., Rogers, T. T., Davies, R. R., Saksida, L. M., Murray, E. A., & Graham, K. S. (2005). Functional specialization in the human medial temporal lobe. *The Journal of Neuroscience*, *25*, 10239-10246. doi: 10.1523/JNEUROSCI.2704-05.2005

Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, *45*, 2963-2974. doi: 10.1016/j.neuropsychologia.2007.05.023

Barense, M. D., Henson, R. N. A., & Graham, K. S. (2011). Perception and conception: temporal lobe activity during complex discriminations of familiar and novel faces and objects. *Journal of Cognitive Neuroscience*, *23*, 3052-3067. doi: 10.1162/jocn_a_00010

Barense, M. D., Henson, R. N. A., Lee, A. C. H., & Graham, K.S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*, 389-401. doi: 10.1002/hipo.20641

Barense, M. D., Rogers, T. T., Bussey, T. J., Saksida, L. M., & Graham, K. S. (2010). Influence of conceptual knowledge on visual object discrimination: insights from semantic dementia and MTL amnesia. *Cerebral Cortex*, *20*, 2568-2582. doi: 10.1093/cercor/bhq004

Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., Pruessner, J. C., Yonelinas, A. P., & Köhler, S. (2007). Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 16382-16387. doi: 10.1073/pnas/0705273104

Buckley, M. J., Booth, M. C., Rolls, E. T., & Gaffan, D. (2001). Selective perceptual impairments after perirhinal cortex ablation. *The Journal of Neuroscience*, *21*, 9824-9836.

Buckley, M. J., & Gaffan, D. (1997). Impairment of visual object-discrimination learning after perirhinal cortex ablation. *Behavioral Neuroscience*, *111*, 467-475. doi: 10.1037/0735-7044.111.3.467

Buckley, M. J., & Gaffan, D. (1998). Perirhinal cortex ablation impairs visual object identification. The *Journal of Neuroscience*, 18, 2268-2275.

Bussey, T. J., & Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus*, *17*, 898-908. doi: 10.1002/hipo.20320

Bussey, T. J., & Saksida, L. M. (2002). The organization of visual object representation: a connectionist model of effects of lesions in perirhinal cortex. The European Journal of Neuroscience, 15, 355-364. doi: 10.1046/j.0953-816x.2001.01850.x

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *The European Journal of Neuroscience*, *15*, 365-374. doi: 10.1046/j.0953-816x.2001.01851.x

Bussey, T. J., Saksida, L. M., & Murray, E.A. (2003). Impairments in visual discrimination after perirhinal cortex lesions: testing 'declarative' vs. 'perceptual-mnemonic' views of perirhinal cortex function. *The European Journal of Neuroscience*, *17*, 649-660. doi: 10.1046/j.1460-9568.2003.02475.x

Bussey, T. J., Saksida, L. M., & Murray, E.A. (2006). Perirhinal cortex and feature-ambiguous discriminations. *Learning & Memory*, *13*, 103-105. doi: 10.1101/lm.163606

Corkin, S., Amaral, D. G., González, R. G., Johnson, K. A., & Hyman, B. T. (1997). H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. *The Journal of Neuroscience*, *17*, 3964-3979.

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *The Journal of Neuroscience*, *26*, 12186-12197. doi: 10.1523/JNEUROSCI.2818-06.2006

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010). Functional dissociations within the ventral object processing pathway: cognitive modules or a hierarchical continuum? *Journal of Cognitive Neuroscience*, *22*, 2460-2479. doi: 10.1162/jocn.2009.21373

Devlin, J. T., & Price, C. J. (2007). Perirhinal contributions to human visual perception. *Current Biology*, *17*, 1484-1488. doi: 10.1016/j.cub.2007.07.066

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends in Cognitive Sciences, 11*, 379-386. doi: 10.1016/j.tics.2007.08.001

Drachman, D. A., & Arbit, J. (1966). Memory and the hippocampal complex. II. Is memory a multiple process? *Archives of Neurology*, *15*, 52-61. doi: 10.1001/archneur.1966.00470130056005

Eacott, M., Gaffan, D., & Murray, E. A. (1994). Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. *The European Journal of Neuroscience*, *6*, 1466-1478.

Eichenbaum, H. (2004). Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron*, *44*, 109-120.

Freiwald, W. A., & Tsao, D. Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, *330*, 845-851. doi: 10.1126/science.1194908

Gaffan, D., & Murray, E. A. (1992). Monkeys (Macaca fascicularis) with rhinal cortex ablations succeed in object discrimination learning despite 24-hr intertrial intervals and fail at matching to sample despite double sample presentations. *Behavioral Neuroscience*, *106*, 30-38. doi: 10.1037/0735-7044.106.1.30

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia*, *45*, 32-41. doi: 10.1016/j.neuropsychologia.2006.04.015

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*, 20-25.

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*, 831-853. doi: 10.1016/j.neuropsychologia.2010.01.001

Haig, N. D. (1984). The effect of feature displacement on face recognition. *Perception*, *13*, 505-512.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*, 223-233.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biological Psychiatry*, *51*, 59-67. doi: http://dx.doi.org/10.1016/S0006-3223(01)01330-0

Hoffman, E. A, & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience*, *3*, 80-84. doi: 10.1038/71152

Holdstock, J. S, Hocking, J., Notley, P., Devlin, J. T., & Price, C. J. (2009). Integrating visual and tactile information in the perirhinal cortex. *Cerebral Cortex*, *19*, 2993-3000. doi: 10.1093/cercor/bhp073

Horel, J. A, Pytko-Joiner, D. E, Voytko, M. L., & Salsbury, K. (1987). The performance of visual tasks while segments of the inferotemporal cortex are suppressed by cold. *Behavioural Brain Research*, *23*, 29-42.

Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *The Journal of Physiology*, *195*, 215-243.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., Laakso, M. P., & Pitkänen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *American Journal of Neuroradiology*, *19*, 659-671.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *The Journal of Neuroscience*, *17*, 4302-4311.

Kanwisher, N. G., & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical transactions of the Royal Society of London Series B, Biological Sciences*, *361*, 2109-2128. doi: 10.1098/rstb.2006.1934

Kesler-West, M. L., Andersen, A. H., Smith, C. D., Avison, M. J., Davis, C. E., Kryscio, R. J., & Blonder, L. X. (2001). Neural substrates of facial emotion processing using fMRI. *Frontiers in Psychology*, *11*, 213-226. doi: 10.3389/fpsyg.2013.00095

Kim, S., Jeneson, A., Van Der Horst, A. S., Frascino, J. C., Hopkins, R. O., & Squire, L. R. (2011). Memory, visual discrimination performance, and the human hippocampus. *The Journal of Neuroscience*, *31*, 2624-2629. doi: 10.1523/JNEUROSCI.5954-10.2011

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends in Cognitive Sciences*, *17*, 26-49.

Lee, A. C. H., Bandelow, S., Schwarzbauer, C., Henson, R. N. A., & Graham, K. S. (2006). Perirhinal cortex activity during visual object discrimination: an event-related fMRI study. *NeuroImage*, *33*, 362-373. doi: 10.1016/j.neuroimage.2006.06.021

Lee, A. C. H., Buckley, M. J., Gaffan, D., Emery, T., Hodges, J. R., & Graham, K. S. (2006). Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: a double dissociation in dementia. *The Journal of Neuroscience*, *26*, 5198-5203. doi: 10.1523/JNEUROSCI.3157-05.2006

Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H., Scahill, V. L., Gaffan, D., Bussey, T. J., Davies, R. R., Kapur, N., Hodges, J. R. and others. (2005).

Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, *15*, 782-797. doi: 10.1002/hipo.20101

Lee, A. C. H., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., Hodges, J. R., & Graham, K. S. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*, *43*, 1-11. doi: 6/j.neuropsychologia.2004.07.017

Lee, A. C. H., Scahill, V. L., & Graham, K. S. (2008). Activating the medial temporal lobe during oddity judgment for faces and scenes. *Cerebral Cortex*, *18*, 683-696. doi: 10.1093/cercor/bhm104

Levy, D., Shrager, Y., & Squire, L. R. (2005). Intact visual discrimination of complex and feature-ambiguous stimuli in the absence of perirhinal cortex. *Learning & Memory*, 12, 61-66. doi: 10.1101/lm.84405

Litman, L., Awipi, T., & Davachi, L. (2009). Category-specificity in the human medial temporal lobe cortex. *Hippocampus*, *19*, 308-319. doi: 10.1002/hipo.20515

Maurer, D., Grand, R., & Mondloch, C. (2002). The many faces of configural processing. *Trends in Cognitive Sciences*, *6*, 255-260.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Montaldi, D., Grigor, J., Gummer, A., Cariga, P., Downes, J. J., Tsivilis, D., Gaffan, D. and others. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus*, *14*, 763-784. doi: 10.1002/hipo.10211

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *The Journal of Neuroscience*, *13*, 5418-5432.

Milner, B. (1962). Physiologie de l'hippocampe, P. Passouant, ed. (Paris: Centre National de la Recherche Scientifique), 257–272.

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, *19*, 421-446.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature*, 273, 297-298. doi: 10.1038/273297a0

Mishkin, M., Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioural Brain Research*, *6*, 57-77.

Moeller, S., Freiwald, W. A., & Tsao, D. Y. (2008). Patches with links: a unified system for processing faces in the macaque temporal lobe. *Science*, *320*, 1355-1359. doi: 10.1126/science.1157436

Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: Complementary findings from amnesia and fMRI. *The Journal of Neuroscience*, *33*, 10490-10502. doi: 10.1523/JNEUROSCI.2958-12.2013

Mundy, M. E., Downing, P. E., & Graham, K. S. (2012). Extrastriate cortex and medial temporal lobe regions respond differentially to visual feature overlap within preferred stimulus category. *Neuropsychologia*, 50, 3053-3061. doi: 10.1016/j.neuropsychologia.2012.07.006

Mur, M., Ruff, D. A., Bodurka, J., Bandettini, P. A., & Kriegeskorte, N. (2010). Face-identity change activation outside the face system: "Release from adaptation" may not always indicate neuronal selectivity. *Cerebral Cortex*, *20*, 2027-2042. doi: 10.1093/cercor/bhp272

Murray, E., & Bussey, T. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Sciences*, *3*, 142-151.

Murray, E. A., & Mishkin, M. (1986). Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. *The Journal of Neuroscience*, *6*, 1991-2003.

Murray, E. A., & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *The Journal of Neuroscience*, *18*, 6568-6582.

Narumoto, J., Okada, T., Sadato, N., Fukui, K., & Yonekura, Y. (2001). Attention to emotion modulates fMRI activity in human right superior temporal sulcus. *Cognitive Brain Research*, *12*, 225-231. doi: http://dx.doi.org/10.1016/S0926-6410(01)00053-2

Nasr, S., & Tootell, R. B. H. (2012). Role of fusiform and anterior temporal cortical areas in facial recognition. *NeuroImage*, *63*, 1743-1753. doi: http://dx.doi.org/10.1016/j.neuroimage.2012.08.031

Nestor, A., Plaut, D. C., & Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 9998-10003. doi: 10.1073/pnas.1102433108

O'Kane, G., Kensinger, E. A., & Corkin, S. (2004). Evidence for semantic learning in profound amnesia: an investigation with patient H.M. *Hippocampus*, *14*, 417-425. doi: 10.1002/hipo.20005

O'Neil, E. B., Cate, A. D., & Köhler, S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *The Journal of Neuroscience*, *29*, 8329-8334. doi: 10.1523/JNEUROSCI.0374-09.2009

Pinsk, M. A., Arcaro, M., Weiner, K. S., Kalkus, J. F., Inati, S. J., Gross, C. G., Kastner, S. (2009). Neural representations of faces and body parts in macaque and human cortex: a comparative fMRI study. *Journal of Neurophysiology*, *101*, 2581-2600. doi: 10.1152/jn.91198.2008

Pitcher, D., Walsh, V., & Duchaine, B. (2011). The role of the occipital face area in the cortical face perception network. *Experimental Brain Research*, *209*, 481-493. doi: 10.1007/s00221-011-2579-1

Puce, A., Allison, T., Asgari, M., Gore, J. C., & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *The Journal of Neuroscience*, *16*¸ 5205-5215.

Rajimehr, R., Young, J. C., & Tootell, R. B. H. (2009). An anterior temporal face patch in human cortex, predicted by macaque maps. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 1995-2000. doi: 10.1073/pnas.0807304106

Rossion, B. (2008). Picture-plane inversion leads to qualitative changes of face perception. *Acta Psychologica*, *128*, 274-289. doi: 10.1016/j.actpsy.2008.02.003

Rossion, B., Hanseeuw, B., & Dricot, L. (2012). Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. *Brain and Cognition, 79*, 138-157. doi: 10.1016/j.bandc.2012.01.001

Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2006). No effect of hippocampal lesions on perirhinal cortex-dependent feature-ambiguous visual discriminations. *Hippocampus*, *16*, 421-430. doi: 10.1002/hipo.20170

Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2007). Impairment and facilitation of transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. *Cerebral Cortex*, *17*, 108-115. doi: 10.1093/cercor/bhj128

Schultz, H., Sommer, T., & Peters, J. (2012). Direct evidence for domain-sensitive functional subregions in human entorhinal cortex. *Journal of Neuroscience*, *32*, 4716-4723. doi: 10.1523/JNEUROSCI.5126-11.2012

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*, 11-21. doi: 10.1136/jnnp.20.1.11

Shrager, Y., Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Intact visual perception in memory-impaired patients with medial temporal lobe lesions. *The Journal of Neuroscience, 26*, 2235-2240. doi: 10.1523/JNEUROSCI.4792-05.2006

Sidman, M., Stoddard, L. T., & Mohr, J. P. (1968). Some additional quantitative observations of immediate memory in a patient with bilateral hippocampal lesions. *Neuropsychologia*, 6, 245-254. doi: 10.1016/0028-3932(68)90023-7

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*, 1380-1386.

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron*, *61*, 6-9. doi: 10.1016/j.neuron.2008.12.023

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279-306. doi: 10.1146/annurev.neuro.27.070203.144130

Squire, L. R., Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annual Review of Neuroscience*, *34*, 259-288. doi: 10.1146/annurev-neuro-061010-113720

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nature Reviews Neuroscience*, *8*, 872-883. doi: 10.1038/nrn2154

Streit, M., Ioannides, A. A., Liu, L., Wölwer, W., Dammers, J., Gross, J., Gaebel, W., & Müller-Gärtner, H. W. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. *Cognitive Brain Research*, *7*, 481-491.

Suzuki, W. A. (2009). Perception and the Medial Temporal Lobe: Evaluating the Current Evidence. *Neuron*, *61*, 657-666. doi: 10.1016/j.neuron.2009.02.008

Suzuki, W. A., & Amaral, D. G. (1994). Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *The Journal of Comparative Neurology*, *350*, 497-533.

Thomas, C., Avidan, G., Humphreys, K., Jung, K. J., Gao, F., & Behrmann, M. (2009). Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nature Neuroscience*\, *12*, 29-31. doi: 10.1038/nn.2224

Tsao, D. Y., Freiwald, W. A., Knutsen, T. A., Mandeville, J. B., & Tootell, R. B. H. (2003). Faces and objects in macaque cerebral cortex. *Nature Neuroscience*, *6*, 989-995. doi: 10.1038/nn1111

Tsao, D. Y., Moeller, S., & Freiwald, W. A. (2008). Comparing face patch systems in macaques and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 19514-19519. doi: 10.1073/pnas.0809662105

Tyler, L. K., Chiu, S., Zhuang, J., Randall, B., Devereux, B. J., Wright, P., Clarke, A., & Taylor, K. I. (2013). Objects and Categories: Feature Statistics and Object

Processing in the Ventral Stream. *The Journal of Cognitive Neuroscience*. doi: 10.1162/jocn_a_00419

Tyler, L. K., Stamatakis, E. A., Bright, P., Acres, K., Abdallah, S., Rodd, J. M., & Moss, H. E. (2004). Processing objects at different levels of specificity. *Journal of Cognitive Neuroscience*, *16*, 351-362. doi: 10.1162/089892904322926692

Ungerleider, L.G. & Mishkin. M. (1982). Two cortical visual systems. In: The analysis of visual behavior (ed. D.J. Ingle, R.J.W. Mansfield, and M.A. Goodale), pp. 549–586. MIT Press, Cambridge, MA.

Von Der Heide, R. J., Skipper, L. M., & Olson, I. R. (2013). Anterior temporal face patches: a meta-analysis and empirical study. *Frontiers in Human Neuroscience*, *7*, 1-18. doi: 10.3389/fnhum.2013.00017

Winston, J. S., Henson, R. N. A., Fine-Goulden, M. R., & Dolan, R. J. (2004). fMRI-Adaptation Reveals Dissociable Neural Representations of Identity and Expression in Face Perception. *The Journal of Neurophysiology*, *92*, 1830-1839. doi: 10.1152/jn.00155.2004

Wixted, J. T., & Squire, L. R. (2010). The role of the human hippocampus in familiarity-based and recollection-based recognition memory. *Behavioural Brain Research*, *215*, 197-208. doi: 10.1016/j.bbr.2010.04.020

Yonelinas, A. P., Kroll, N. E. A., Quamme, J. R., Lazzara, M. M., Sauvé, M. J., Widaman, K. F., & Knight, R. T. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience*, *5*, 1236-1241. doi: 10.1038/nn961

Zola-Morgan, S., Squire, L. R., Amaral, D. G., & Suzuki, W. A. (1989). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *The Journal of Neuroscience*, *9*, 4355-4370.

Zola-Morgan, S., Squire, L. R., & Ramus, S. J. (1994). Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. *Hippocampus*, *4*, 483-495. doi: 10.1002/hipo.450040410

Zola-Morgan, S., Squire, L. R. (1986). Memory impariment in monkeys following lesions limited to the hippocampus. *Behavoral Neuroscience*, *100*, 155-160. doi: 10.1037/0735-7044.100.2.155

Chapter 2

2 Representational Demands Modulate Involvement of Perirhinal Cortex in Face Processing[1]

2.1 Introduction

The capacity of the brain to generate internal neural representations of objects in the external world is critical for the perception of the present environment, as well as for memory of past object encounters. It is well established that the integrity of the medial temporal lobe (MTL) is critical for declarative memory functioning (Milner et al., 1998). The MTL, which consists of the hippocampus, entorhinal, perirhinal, and parahippocampal cortex, is widely connected with the neocortex; perirhinal cortex (PrC) receives much of its neocortical input from unimodal association areas, including significant contributions from infero-temporal regions in the ventral visual pathway that carry information about object features (Suzuki and Amaral, 1994; Kahn et al., 2008). Many sources of evidence have led to a consensus that PrC plays an essential role in the recognition of prior occurrence of objects (see Brown et al., 2010 for recent review). However, some recent studies cast doubt on the classic notion that the contributions of PrC to object processing are limited to mnemonic functions; findings from functional neuroimaging and lesion research in human and nonhuman species also point to a role of PrC in online processing for visual perceptual tasks, in which all stimuli remain visible throughout trial execution. This evidence remains highly controversial at present (see Baxter, 2009; Suzuki and Baxter, 2009; Knutson et al., 2012; Lee et al., 2012). Given that it challenges the fundamental conception that the functional role of the MTL, as a declarative memory system, can be clearly distinguished from that of the ventral visual

[1] A version of this chapter has recently been published. O'Neil E. B., Barkley V. A., & Köhler S. (2013).

pathway as a perceptual system (Buckley and Gaffan, 2006; Murray et al., 2007; Baxter, 2009), addressing this issue is of critical importance to understanding brain organization more broadly.

A functional characterization of MTL structures that is radically different from the declarative-memory account emphasizes the specific types of neural representations these structures support (Bussey and Saksida, 2007; Murray et al., 2007; Graham et al., 2010; Lee et al., 2012). Within such a framework, PrC has been proposed to constitute an extension of the representational hierarchy within the ventral visual pathway for object identification. PrC may provide a representation of complex conjunctions of features (Murray and Bussey, 1999; Buckley and Gaffan, 2006; Murray et al., 2007), or of gestalt-characteristics of objects (Cate and Köhler, 2006; O'Neil et al., 2009) that are more integrated than representations in the ventral visual pathway upstream, and that are critical when individual features or simple feature conjunctions are insufficient for the discrimination at hand. Following this account, recruitment of PrC hinges on a convergence of two factors (Cowell et al., 2010). First, an object must share features with other stimuli such that it can only be distinguished from these stimuli when features are considered at the level of conjunctions or even more highly integrated object representations. Second, the specific task demands must be such that successful performance necessitates the use of these representations and cannot be based on simple features supported by ventral regions upstream.

Human faces constitute a stimulus class that is of particular relevance for examining the representational account of MTL functioning. Unlike many other object classes, faces always share a basic configuration, sometimes referred to as first-order relationships, which consists of two eyes above a nose above a mouth (see Maurer et al., 2002 for elaboration). Classification of a visual stimulus as a face relies on detection of this basic configuration. Despite the fact that all faces share a set of basic features in a common configuration, humans are very adept at assigning unique identities to individual faces, and at recognizing their prior occurrence. To achieve individuation, it is thought that the perceptual system exploits information relating to second-order relationships, that is, the small differences in the spacing of facial features within the basic configuration

that are present across individuals, as well as subtle differences in feature shape and texture. Considerable evidence also implicates holistic representations with Gestalt characteristics, in which the whole is more than the sum of its parts, in face individuation (see Farah et al., 1998; Rossion, 2009, for reviews).

A classic demonstration of the critical role of highly integrated representations in face recognition is the face inversion effect, which reflects the observation that the rotation of a face by 180° in the picture plane impairs performance on many perceptual and memory tasks to a greater extent than other stimulus classes (Yin, 1969; see Maurer et al., 2002; Rossion, 2009 for reviews;). The precise mechanisms responsible for the face inversion effect remain a matter of debate in the literature, with some positing that inversion disrupts holistic processing, and others emphasizing the impact on processing of second-order relationships. Across different accounts, however, there seems to be an agreement that the effect highlights a critical role for integrated face representations, extending beyond that of individual features, in performance on the tasks with which it can be revealed. This property makes face inversion a particularly promising manipulation to probe the nature of representations supported by PrC.

Although a comprehensive review of research on the neural underpinnings of face processing is beyond the scope of the present article, it is fair to say that most investigations have focused on the role of regions in the ventral visual pathway that are located more posteriorly than PrC, with most emphasis on the middle fusiform gyrus (fusiform face area, FFA) but additional consideration of aspects of inferior occipital cortex (occipital face area, OFA) and the posterior part of the superior temporal sulcus (for reviews, see Gobbini and Haxby, 2007; Fox et al., 2008; Atkinson and Adolphs, 2011). Concerning face inversion effects in the FFA, human fMRI findings have been somewhat mixed (see Rossion and Gauthier, 2002 for review). Although some authors report a reduced response in the FFA for inverted as compared to upright faces (e.g., Kanwisher et al., 1998; Gauthier et al., 1999; Haxby et al., 1999; James et al., 2012), other studies have failed to reveal inversion effects within this functionally defined region (e.g., Aguirre et al., 1999; Epstein et al., 2006), or in the vicinity of FFA when examining whole brain effects (Leube et al., 2003; Epstein et al., 2006). Attempts

to correlate, across subjects, the magnitude of behavioral inversion effects with changes in FFA BOLD activation also point to mixed findings. Yovel and Kanwisher (2005) found evidence for a relationship between FFA activity and the behavioral inversion effect; however, a subsequent study did not demonstrate this effect (Epstein et al., 2006). Variations in the specific task demands and issues relating to statistical power may explain some of these divergent findings. Regardless, effects of stimulus inversion have also been revealed in other ventral visual pathway regions (e.g., Haxby et al.,1999; Epstein et al., 2006; Nasr and Tootell, 2012), pointing to the benefits of going beyond the FFA in efforts to advance our understanding of this effect.

A number of studies based on electrophysiological recordings and fMRI in nonhuman primates have identified "face-patches" in the anterior temporal lobe, which exhibit a preferential response to faces as compared to other types of visual stimuli (Tsao et al., 2003; Pinsk et al., 2005; Rajimehr et al., 2009; Freiwald and Tsao, 2010). Micro-stimulation of neurons in face patches during fMRI scanning has been shown to produce changes in the BOLD response in other face patches, pointing to a distributed, highly interconnected network of face-processing regions in the ventral visual pathway (Moeller et al., 2008). Parallel studies conducted with fMRI in human and nonhuman primates point to a human homologue of the anterior temporal face patch in the anterior (rostral) collateral sulcus in what appears to be PrC (Tsao et al., 2008; Rajimehr et al., 2009). This finding has also been confirmed in a large-scale fMRI study that was based on a functional-localizer design of the kind typically employed to identify the FFA in the fusiform gyrus (Rossion et al., 2012). The authors of that study employed a one-back working-memory task, and compared brain responses to faces with responses to cars and corresponding scrambled images. They found increased responses to faces in a number of regions outside the classic ventral visual face-processing network, including in right PrC (see also Nasr and Tootell, 2012). In further research, a differential role of PrC in face processing has also been reported based on comparisons between faces and scenes, and based on the use of other tasks, including recognition-memory and perceptual-discrimination judgments (Lee et al., 2005; Taylor et al., 2007; Lee et al., 2008; Barense et al., 2010).

In a recent study from our lab (O'Neil et al., 2009), we examined activity in PrC while participants completed forced-choice tasks with presentations of three highly similar morphed faces. An oddity task required the selection of the face most different from the others in the display, while a recognition-memory task required the selection of the item presented in an earlier study phase. When compared against a baseline task that involved luminance judgments of comparable difficulty without any presentation of faces, both tasks showed a comparable increase in right PrC activity. Furthermore, right PrC activity was also found to be greater for accurate than inaccurate trials in both tasks. Subsequent examination of functional connectivity between PrC and other cortical regions revealed that differences between these two tasks emerge at the level of functional interactions, rather than PrC involvement as such (O'Neil et al., 2012). Together, these findings demonstrate that faces represent a class of visual stimuli that easily engages PrC mechanisms, specifically in the right hemisphere. They also suggest that PrC involvement is not limited to declarative-memory tasks in which reference to a distinct prior study phase is required.

Although the evidence reviewed provides converging evidence that PrC is involved in face processing, the specific functional role it plays remains poorly understood at present. A hint that this role may pertain to demands for highly integrated and differentiated representations is offered by recent fMRI findings showing increased PrC activity when participants make perceptual discriminations between faces presented from different as compared to identical viewpoints (Barense et al., 2010; see Freiwald and Tsao, 2010, for related evidence in neurophysiological recordings in the anterior medial face patch). In the present fMRI study, we aimed to shed further light on the representational demands that influence PrC involvement in mnemonic and perceptual discriminations of faces. We independently manipulated the nature of the task to be performed and the stimuli presented. At the task level, we compared a recognition-memory and a perceptual-oddity task with a feature-search task. All tasks involved presentation of the same type of highly similar morphed face stimuli. Only the first two tasks, however, required individuation of these faces; the feature-search task could be solved based on the detection of a simple visual feature without discriminating between the faces as a whole. At the stimulus level, we manipulated the orientation of the stimuli through face inversion on half of the trials

across all tasks. Critically, this set-up allowed us to hold stimulus complexity constant across all experimental conditions. We hypothesized that PrC activity would reflect task and stimulus demands related to the need to generate highly integrated face representations. Based on differential demands for face individuation, we expected an increased role of PrC in the perceptual-oddity and recognition-memory tasks as compared to the feature-search task. Additionally, we predicted that the orientation manipulation would preferentially affect perceptual-oddity and recognition-memory tasks, with upright face stimuli facilitating the generation of an integrated stimulus representation and, thus, increasing recruitment of PrC. Although our primary focus was on PrC, we also conducted multivariate whole-brain analyses to examine to what extent PrC was embedded in larger networks of regions, including other components of the ventral visual pathway, that responded to our experimental manipulations.

2.2 Materials and Methods

2.2.1 Participants

Sixteen healthy right-handed university students (six male, age range = 20–31 yr) with normal or corrected-to-normal vision participated in the study. All participants gave written informed consent, and received compensation for their participation. This study received approval from the Health Sciences Research Ethics Board at the University of Western Ontario.

2.2.2 Materials

Stimuli were selected from a set of images previously created to examine the role of PrC in related research (O'Neil et al., 2009). Stimulus triplets for the experimental tasks were generated by designating two trial-unique color photographs of Caucasian faces with neutral expressions as endpoints on a 100-step morph continuum. For perceptual-oddity trials, triplet members were captured at different points on this continuum (i.e., step 30, 53, and 97), such that the distance between the oddball image and its neighbor was larger (44 steps) than the distance between the other two images (23 steps). In contrast, triplet members for the recognition-memory and feature-search tasks were equally spaced along

the morph continuum (step 5, 50, and 95). In trials of the feature-search task, a small semitransparent (6% opacity) circle was superimposed on one of the three morphed faces. This circle was divided into four quadrants, with one pair of opposing quadrants shaded white and the other shaded black (Fig. 2.1). Locations of the circle were restricted to be on the flesh of the face excluding locations on eyebrow, nostrils, and other non-flesh face components. The assignment of the trial unique face triplets to specific task conditions was counterbalanced across participants, as was the location of the correct item within the stimulus arrays. In the luminance baseline task two identical squares, and a third with 4% greater luminance were presented against a visual noise background. Luminance levels for each array of squares varied across trials.

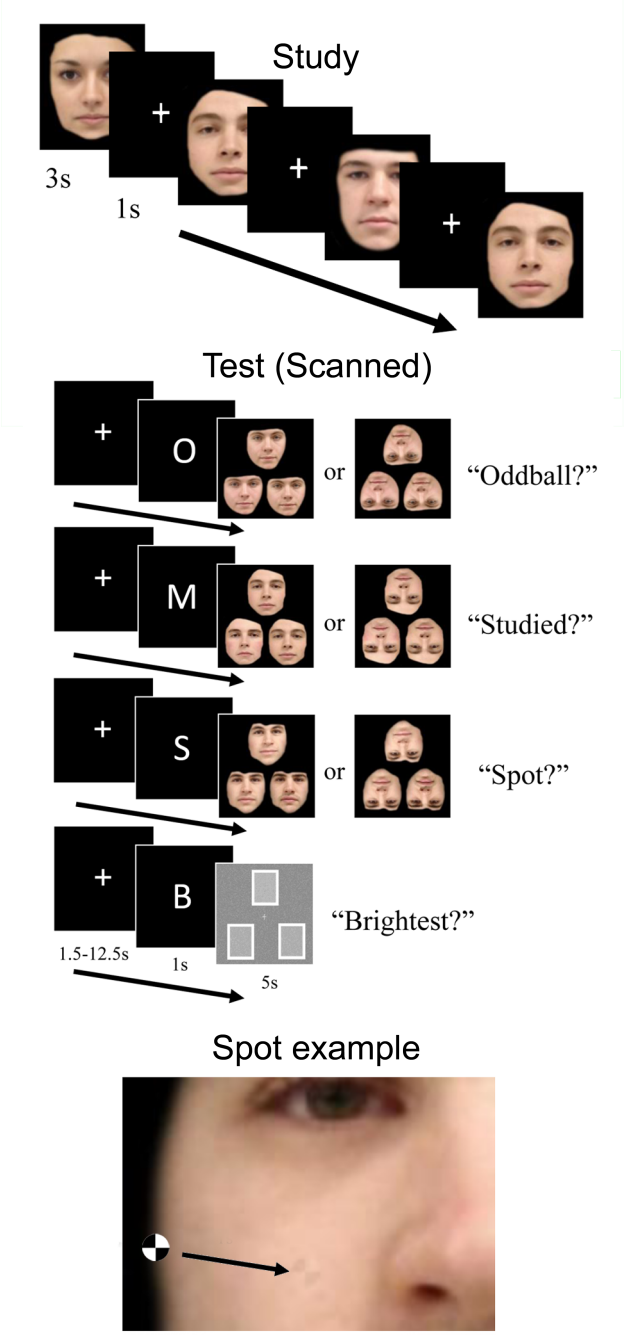

Figure 2.1. Experimental design. Each experimental run consisted of an initial study phase (pre-scanning) that required memorization of a series of faces in upright or inverted orientation. Under scanning, participants made perceptual oddity (O), forced-choice recognition memory (M), and feature-search (S) judgments on upright or inverted stimuli. For the luminance baseline task, participants selected the brightest of three squares.

2.2.3 Experimental Tasks and Procedures

The experiment was divided into eight study-test runs. Participants viewed the stimulus displays through a mirror at an approximate size of 22 × 19° visual angle and responses were made using an MRI-compatible keypad.

All experimental tasks required the selection of a target from a stimulus array of three highly similar morphed faces that were presented simultaneously (Fig. 1). In the forced-choice recognition-memory task, participants were asked to select the face they had encountered previously in a study phase prior to scanning. In the perceptual-oddity task, they were required to select the face most different from the other two (i.e., the "oddball"). In the third experimental task, participants were asked to search for an artificial mole (i.e., a small, semitransparent circular pattern introduced to participants prior to scanning) superimposed on one of the three faces; this feature-search task was the only task designed to require no engagement of configural or holistic face representations in our experimental set-up.

Prior to each run, a study phase took place in the scanner that included the presentation of nine faces that served as targets for the recognition-memory trials in the corresponding run. Stimuli were presented three times each, in a random order, with memorization instructions. Each presentation was 3,000 ms in duration with a 1,000 ms intertrial interval. During scanning, each run included trials from all tasks that were intermixed in a fast-event related design. Every run included nine trials from the three experimental tasks (perceptual-oddity, recognition-memory, and feature-search tasks) and five trials from the luminance baseline task. A letter cue was presented for 1,000 ms at the onset of each trial to indicate the type of task to follow. This was followed by a 5,000 ms presentation of the three-item stimulus array, followed by a jittered fixation with a range between 1.5 and 13.5 s. Order of trials and jitter between trials within each run were optimized using the OptSeq2 algorithm (http://surfer.nmr.mgh.harvard.edu/optseq/).

One of the critical manipulations of theoretical interest concerned the inversion of faces in our experimental tasks. Behavioral piloting revealed that inter-mixed presentation of faces in upright and inverted orientation within the same run resulted in

chance performance across the three experimental tasks, which would make interpretation of any related fMRI findings difficult. To obtain performance at a level above chance, trials were presented in a single orientation across experimental tasks in each run. Thus, four of the eight fMRI runs were comprised of displays of faces in upright orientation, and the remaining runs involved presentation of faces in an inverted orientation. Participants received one of two run orders, arranged such that the mean positions of runs with upright and inverted stimuli were equated within the entire scanning session. All faces in the upright condition were presented upright both at study and at test. For two of the four runs that included presentation of inverted faces, the faces displayed for study (i.e., memorization) prior to scanning were in an upright orientation, and for the other two runs they were in an inverted orientation. This arrangement was included in the design to ensure that any observed behavioral effects of inversion could not be attributed to a mismatch in the orientation of stimuli between study and test. However, a repeated measures *t*-test of the data collected during scanning revealed no effect of orientation at study on behavioral performance in the recognition-memory task for inverted faces at test $t(15) = -1.28$, $P > 0.2$. This is in line with another recent study that examined the orientation match between study and test in face recognition (Marzi and Viggiano, 2011). Recent research demonstrates that the extent to which a study-test match supports retrieval is modulated by the degree to which a cue provides diagnostic information about a studied item (e.g., Goh and Lu, 2012; Poirier et al., 2012; see Nairne, 2002 for related discussion). Compared to upright face cues, presentation of inverted face cues increases reliance on feature-based processing, in particular under the conditions of the current study in which image morphing introduced many overlapping features between the three faces in each display. These features limit the diagnostic value of the cues, and consequently, the benefit of a study-test match in the inverted cue condition. Given our behavioral findings and these theoretical considerations, trials were ultimately collapsed across study orientation for all fMRI analyses. Collapsing across study orientation also allowed us to equate the number of trials considered in our fMRI analyses across all experimental conditions.

2.2.4 Functional Localizer Tasks

To determine the extent to which PrC would exhibit a preference for face stimuli, as suggested by some of the neuroimaging and electrophysiological research reviewed in the Introduction, two functional-localizer runs were included as well. These runs followed a protocol that has previously been used in several other studies from our lab (e.g., Ganel et al., 2006; O'Neil et al., 2009; Cate et al., 2011) and is similar to that used in many other studies in the visual cognition literature more broadly. It involved presentation of grayscale faces, common objects, and places (buildings and landscapes) under passive viewing instructions. Stimuli from each category were presented in a blocked manner with alternating blocks of scrambled images corresponding to each stimulus category.

2.2.5 MRI Acquisition

All MRI data were acquired on a 3-Tesla Siemens TIM MAGENTOM Trio scanner. T1-weighted anatomical images were obtained using an ADNI MPRAGE sequence [192 slices, time to repetition (TR) = 2,300 ms, field of view (FOV) = 240 mm × 256 mm, matrix size = 240 × 256, flip angle = 9°, echo time (TE) = 4.25 ms, 1 mm isotropic voxels]. Functional MRI volumes were collected using a T_2*-weighted single-shot gradient-echo-planar acquisition sequence [TR = 2500 ms, TE = 25 ms, slice thickness = 2.5 mm, in-plane resolution = 2.5 mm × 2.5 mm, FOV = 200 mm × 200 mm, matrix size 80 × 80, flip angle = 60°]. Each functional volume included 49 contiguous slices. To optimize MR signal in the anterior temporal lobes, an oblique coronal orientation was selected, with an effort to prevent inclusion of the eyes in slices capturing this region. This slice plan resulted in full coverage of occipital and temporal lobes in all subjects, with inferior aspects of frontopolar cortex, as well as the most superior aspects of parietal cortex not covered in some subjects. For each experimental run, 160 volumes were collected. Each localizer run involved the acquisition of 144 functional volumes.

2.2.6 Univariate Analysis

Preprocessing and univariate analyses were completed using BrainVoyager QX version 2.3 (Brain Innovation). Functional images for all analyses were resampled into 3 mm

isotropic voxels, slice-scan time corrected, three-dimensional (3D) motion corrected to the functional volume taken just prior to the anatomical scan, and high-pass filtered using a Fourier basis set of 2 cycles/run (including linear trend). Images were then coregistered with the anatomical image, transformed into standardized Talairach space and smoothed using a 3D Gaussian kernel with a full-width at half maximum of 8 mm.

For univariate analyses, data were convolved using a double gamma hemodynamic response function (Friston et al., 1998) and examined using a random effects GLM with trials coded by condition, irrespective of accuracy. Regressors were uniquely specified for each combination of task and orientation at test except for the luminance baseline task, which did not include an orientation manipulation; mean image intensity was included as a covariate-of-no-interest in these analyses. Univariate analyses on PrC activity were thresholded at $P < 0.001$ (whole brain, uncorrected), with a minimum cluster size of 27 interpolated 1 mm voxels, corresponding to one functional isotropic 3 mm voxel. Localization of activation in PrC was established at the group level using group-averaged structural (T_1 weighted) MR images, and confirmed through overlay on representative structural images of individual participants. The anatomical boundaries employed were those specified by Pruessner et al. (2002) in a well-established neuroanatomical protocol for volumetric assessment of MTL structures.

2.2.7 Multivariate Analysis

To investigate the relationship between our experimental conditions and fMRI data at the whole-brain level, we used partial least squares (PLS) analysis, a well-established multivariate analysis technique that is based on non-parametric statistics (McIntosh et al., 1996; Krishnan et al., 2011). For PLS analysis, no a priori hemodynamic response function is modeled. Instead, a response window is defined. To this end, a matrix of voxel intensities capturing a temporal window of 15 s following stimulus onset for each trial was constructed. Task PLS uses singular value decomposition to rotate the data matrix to reveal the major sources of task-related differences in activity across the entire functional volume, expressed as latent variables (LVs). As our aim was to test specific effects of interest, we applied a nonrotated version of Task PLS, in which a priori

contrasts restrict the patterns derived (McIntosh et al., 2004; Protzner and McIntosh, 2009). In nonrotated task PLS, a singular image is computed for each contrast of interest, representing the distributed voxel pattern that embodies it. The strength of the relationship between the singular image and the designated contrast is given by the singular value. In this nonrotated version, the singular image is simply the cross product of the contrast and the data matrix, and the singular value is the sum of squared voxel values for the singular image. Statistical assessment was performed using non-parametric permutation tests for the LVs and bootstrap estimation of standard errors for the voxel saliences (i.e., the contributions of specific voxels to the singular image). The permutation test assesses whether the pattern represented in a given LV, captured by the singular value, is sufficiently strong to be considered different from random noise. The standard error estimates of the voxel saliences in each singular image from the bootstrap tests served for assessment of the reliability of the non-zero saliences in significant LVs. Following established criteria for non-parametric tests in PLS analyses, results from the permutation tests were considered significant if they survived $P < 0.05$ (as no correction for multiple comparisons is required; see McIntosh et al., 2004; Stevens et al., 2008; Chen et al., 2009; Protzner and McIntosh, 2009; Krishnan et al., 2011). Saliences were considered significant if they met a threshold of 3.50, corresponding to approximately $P < 0.0005$, at a cluster threshold of five 3 mm isotropic voxels. All PLS results were assessed for statistical significance using 500 permutations and 100 bootstraps.

2.3 Results

2.3.1 Behavioral Results

We first sought to confirm behaviorally that the recognition-memory and perceptual-oddity tasks, but not the feature-search task, were sensitive to the inversion manipulation. Consistent with our predictions, a 3 × 2 (task by orientation) repeated measures ANOVA revealed a significant interaction, $F(2,30) = 19.40$, $P < 0.005$ (Fig. 2.2). Bonferroni corrected pair-wise comparisons showed a detrimental effect of inversion for the recognition-memory $t(15) = 8.30$, $P < 0.005$, and the perceptual-oddity task, $t(15) =$

3.28, $P < 0.005$, but not for the feature-search task, $t(15) = -0.837$, $P > 0.2$. Moreover, the inversion effect was larger for the recognition-memory task than for the perceptual-oddity task, $t(15) = 4.30$, $P < 0.005$. Table 2.1 displays the corresponding reaction time data. A 3 × 2 (task by orientation) repeated measures ANOVA on reaction times revealed a significant interaction, $F(2,30) = 5.57$, $P < 0.01$, but no main effect of orientation $F(1,15) = 0.025$, $P > 0.1$). Bonferroni corrected pair-wise comparisons did not reveal any within-task effects of orientation (all p's > .1). Notably, foreshadowing our fMRI findings, none of the effects revealed in PrC mirrored the pattern of RTs across experimental conditions, arguing against any interpretation in terms of time-on-task effects.

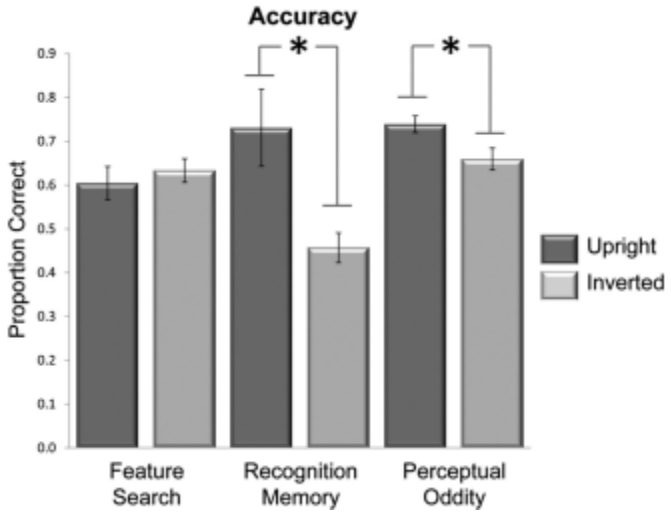

Figure 2.2. Mean accuracy for each condition as measured by proportion correct responses. Note that chance is 0.33. Asterisks denote tasks for which inversion had a significant effect on accuracy. Error bars indicate SEM.

Table 2.1.

Response latencies for the different experimental conditions

Task	Upright	Inverted
Memory	3016(349)	3201(352)
Oddity	2992(624)	2998(380)
Feature Search	3476(430)	3339(330)
Luminance	2542(581)	

Note. Reaction times presented in ms, with standard deviation indicated in parentheses.

2.3.2 Univariate Analyses of fMRI responses in PrC

In the first step of our data analyses, we used a GLM with the goal to replicate our previously reported differential involvement of right PrC in recognition-memory and perceptual-oddity judgments for upright faces, as compared to the luminance baseline task (O'Neil et al.,2009). Note that this and all subsequent univariate analyses were voxel-based rather than based on averaged activity in a predefined region of interest. Consistent with our previous findings, a conjunction (Nichols et al., 2005) of the two contrasts [("upright recognition memory" > "luminance") AND ("upright oddity" > "luminance")], confirmed a differential response in aspects of right PrC ($P < .001$ for each contrast; cluster size = 75 voxels, peak voxel $t(15) = 4.63$, $x = 31$, $y = -2$, $z = -30$). Next, we determined whether PrC would show a differential response for those tasks that required individuation as compared to the task that could be performed based on single features. Toward this end, we conducted another GLM conjunction analysis, in which the luminance baseline task was replaced by the feature-search task with upright faces. This conjunction again revealed a region in right PrC, with a peak voxel identical to that in the previous conjunction analysis (cluster size = 139 voxels, peak voxel $t(15) = 5.24$, $x = 31$, $y = -2$, $z = -30$). This effect supports our hypothesis that right PrC involvement in face processing does not reflect a stimulus-driven response to the presentation of faces per se, but rather, a requirement for specific types of representations as dictated by unique task demands. Figure 2.3 displays the right PrC region identified with our experimental contrasts and its corresponding response profile. Next, we determined whether this task effect was present for both stimulus orientations. A conjunction analysis with the contrasts [("upright recognition memory"+ "upright oddity") > "upright feature search"] AND [("inverted recognition memory"+ "inverted oddity") > "inverted feature search"] revealed a significant task effect at $P < .001$ for the individual contrasts (cluster size 586, peak voxel $t(15) = 6.06$, $x = 31$, $y = -2$, $z = -30$; see Fig. 2.3).

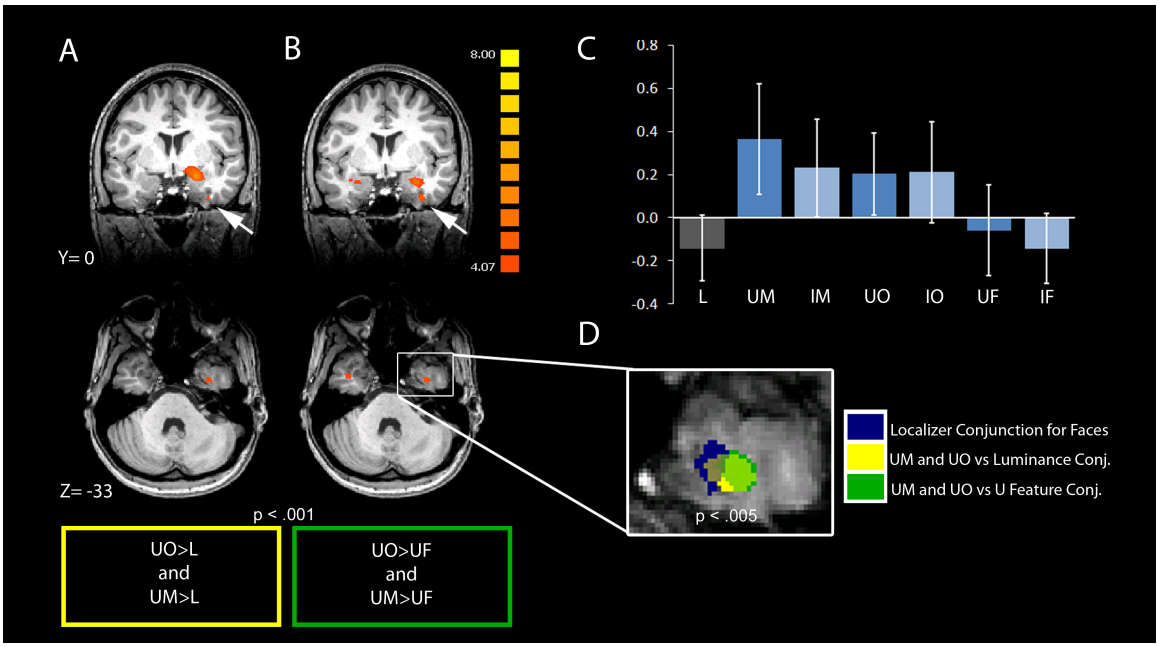

Figure 2.3. Contrasts demonstrating increased PrC activity for oddity and memory tasks. (A) MTL regions reflecting the conjunction of upright memory > luminance AND upright oddity > luminance contrasts ($P < 0.001$ for each contrast). (B) MTL regions reflecting the conjunction of [(upright memory > upright feature search) AND (upright oddity > upright feature search)] contrasts ($P < 0.001$ for each contrast). (C) Beta weights extracted from right PrC voxels active in both luminance conjunction and feature-search conjunction analyses. Error bars reflect 95% confidence intervals. (D) Transverse slice showing overlap of regions identified using the luminance conjunction, feature-search conjunction, as well as localizer conjunction [(faces>places and objects) AND (faces>scrambled images)], each map thresholded at $P < 0.005$ for display purposes, right5right (L-Luminance baseline, M-Recognition-memory, O-Perceptual oddity, F-Feature search, U-Upright, I-Inverted).

When we turned to an examination of the effects of the inversion manipulation, we first addressed whether any PrC response would follow the pattern of behavior across the two tasks with individuation demands. A GLM conjunction analysis, probed with the two contrasts [("upright recognition memory" > "inverted recognition memory") AND ("upright oddity" > "inverted oddity")], revealed no activity in right PrC, even when individual contrasts were examined at a lowered threshold of $P < 0.05$ (which would be justified based on the fact that these contrasts are based on independent observations). Furthermore, we also did not find any response in PrC that reflected a main effect of stimulus orientation across all three tasks even when the critical threshold was lowered to $P < 0.05$ in right PrC. In subsequent analyses, we addressed the possibility that orientation effects may be task specific in a more targeted manner. Given the clear consensus in the literature regarding involvement of PrC in recognition-memory tasks for stimuli presented in an upright orientation, we examined whether PrC might show a differential involvement in upright memory as compared to all five other experimental conditions. This contrast did reveal a large cluster of voxels in right PrC, in the same general area in which our other experimental effects emerged (cluster size = 460, $t(15) = 5.11$, $x = 34$, $y = 1$, $z = -30$). When we assessed whether this pattern across all experimental conditions also reflects, more specifically, increased activity in the upright as compared to the inverted memory condition, we found such an effect for the peak-voxel at a more lenient threshold of $P < 0.05$, $t(15) = 2.22$. We note that this effect of orientation in right PrC response was weaker than the effect we observed for our task manipulation, and was only revealed with this post hoc analysis that followed the general GLM contrast (or the corresponding multivariate PLS contrast summarized below) across all experimental conditions. A corresponding analysis examining a possible differential involvement for the upright perceptual-oddity condition as compared to all other experimental conditions did not reveal any activation in right PrC, even at $P < 0.05$.

2.3.3 Comparison of Experimental Effects in PrC with Functional Localizer Results

Given past reports of a face patch in PrC, we also determined whether the right PrC region that showed the task effect in relation to individuation demands might show

overlap with any region in PrC that could be identified with our independent functional-localizer scans. Using a group level random effects analysis, preference for face stimuli was determined by identifying voxels whose response profile fulfilled two criteria, namely (i) an increase in the BOLD response for faces as compared to scrambled images, and (ii) an increase in the BOLD response for faces as compared to objects and places. Applying a threshold of $P < 0.005$ for individual contrasts in this localizer conjunction, this analysis revealed, consistent with previous reports (Rossion et al., 2012), an area in right PrC that showed face preference, peak voxel: $x = 24$, $y = 1$, $z = -33$, $t(15) = 3.89$, cluster size = 137 voxels. We then superimposed the statistical maps for the most revealing contrasts of our experimental tasks, [("upright recognition memory" > "upright feature search task") AND ("upright oddity" > "upright feature search")], as well as [("upright recognition memory" > "luminance baseline") AND ("upright oddity" > "luminance baseline")], with the conjunction contrast from our functional localizer. Visual inspection of Figure 2.3 reveals that there is indeed clear overlap in right PrC between the experimental and the localizer effects.

2.3.4 Multivariate fMRI analyses

Given the strong evidence from functional neuroimaging and neurophysiological research for distributed face representations in the ventral visual pathway (Haxby et al., 2000; Ishai, 2008; Rossion et al., 2012), we also assessed the effects of our experimental manipulation in regions beyond PrC at the whole brain level. Toward this end, we turned to a multivariate PLS approach, which allowed for identification of spatio-temporal patterns of activity across the brain that relate to our task and orientation manipulations (McIntosh et al.,1996; Krishnan et al., 2011). Here, we focused on three contrasts of interest.

In the first contrast, we aimed to determine whether right PrC is part of a larger network of regions that show a differential response to the requirement of face individuation across our three tasks. To this end, the recognition-memory and perceptual-oddity tasks were contrasted with the feature-search and the luminance baseline tasks across both stimulus orientations. The LV that was associated with this contrast was

found to be significant (singular value = 45.09, $P < 0.001$, see Fig. 2.4). Beyond right PrC, this pattern also included a number of other regions that have previously been linked to face processing, including aspects of the right middle fusiform gyrus in the vicinity of the FFA and the right amygdala (see Table 2.2 for a full listing of local maxima).

With our second contrast we aimed to determine whether the differential response to upright faces in the recognition-memory task, as compared to all other experimental conditions was also present in a pattern of regions beyond right PrC. Again, the LV that was associated with this contrast was found to be significant (singular value = 25.73, $P < 0.001$, see Fig. 2.5 and Table 2.3). The pattern of regions with higher responses for recognition memory judgments on upright faces, as expected based on our univariate analyses, included right PrC; it also covered a number of other regions, such as the right superior temporal sulcus, amygdala, and fusiform gyrus. When we set up a third contrast to examine whether any regions showed an orientation effect for the two tasks with high individuation demands (recognition-memory and perceptual-oddity), but not for the feature-search task, the corresponding LV was not significant (singular value = 17.47, $P > 0.2$). This null result paralleled our pattern of findings in univariate analyses that focused on PrC specifically.

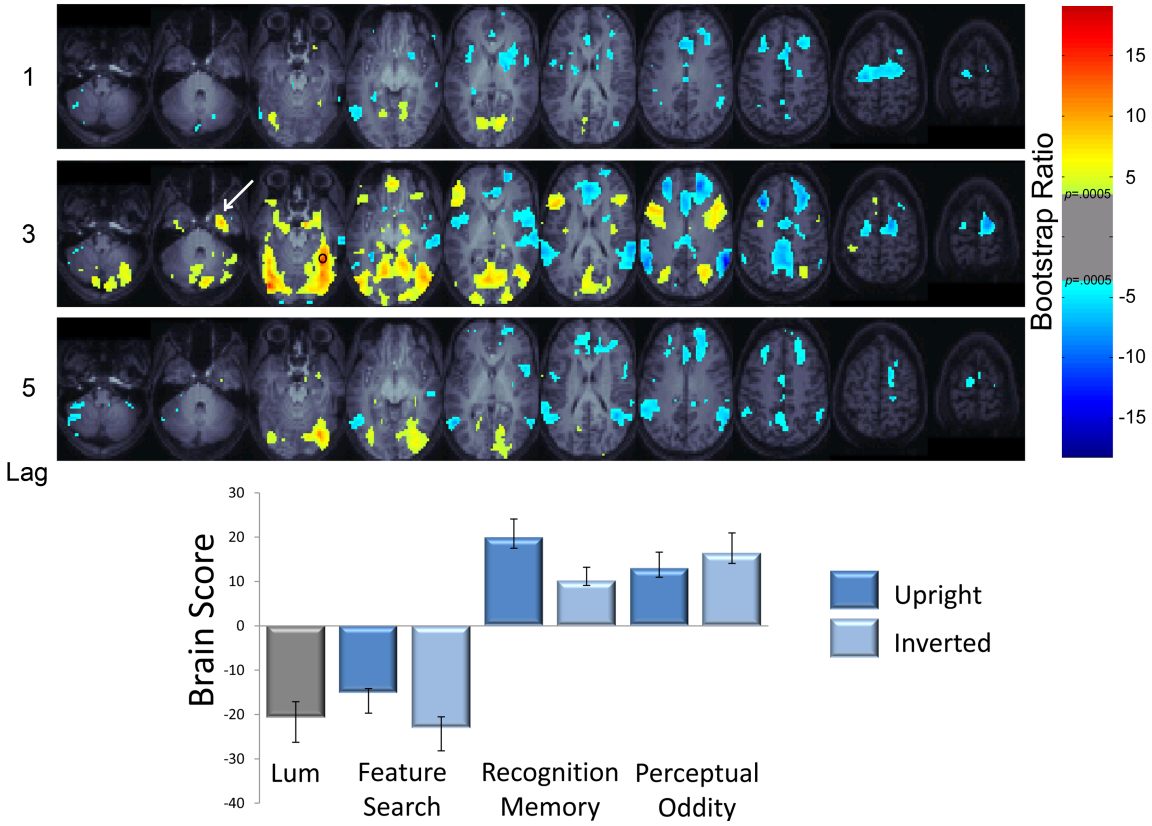

Figure 2.4. LV and associated saliences for PLS task contrast based on individuation demands. Lags 1-5 correspond to 2.5 s intervals encompassing the duration of the hemodynamic response within a trial. Error bars represent 95% confidence intervals derived by bootstrap estimation. White arrow at lag 3 indicates right PrC, black circle denotes peak of right FFA as determined by the univariate analysis of the localizer data.

Table 2.2.

Regions showing reliable saliences for the LV that contrasted the memory and oddity tasks vs. search and luminance tasks

Region	X	y	z	Bootstrap Ratio	Cluster Size (voxels)
	Talairach Coordinates				
Memory and Oddity > Search and Luminance					
Fusiform Gyrus	35	-49	-17	15.41	5255
PrC	29	-1	-26	12.65	323
Amygdala	11	-4	-14	8.17	
Inferior Frontal Gyrus	-46	26	13	12.62	994
Amygdala	-22	-7	-14	6.79	
Middle Frontal Gyrus	41	17	28	9.49	533
Orbital Frontal Gyrus	-4	38	-11	7.51	133
Angular Gyrus	-31	-61	34	6.77	114
Superior Frontal Gyrus	-7	14	49	6.64	71
Insula	-34	-10	19	6.06	15
Postcentral Gyrus	-37	-31	49	5.57	46
PrC	-34	-10	-26	5.35	25
Orbital Frontal Gyrus	35	35	1	5.28	64
Search and Luminance > Memory and Oddity					
Superior Frontal Gyrus	20	44	34	-18.24	2645
Supramarginal Gyrus	56	-52	34	-16.09	1135
Supramarginal Gyrus	-55	-46	34	-10.42	488
Posterior Hippocampus/ Parahippocampal Gyrus	-34	-40	-5	-7.01	22
Orbital Frontal	-16	14	-8	-6.59	22
Middle Frontal Gyrus	-22	-13	58	-6.56	136
Superior Frontal Gyrus	-52	-1	7	-6.11	150
Insula	-37	-16	-2	-4.96	19
Middle Temporal Gyrus	-55	-52	-5	-4.85	15

Note. Talairach coordinates indicate peak voxel. Bootstrap ratios all reflect minimum significance of $P < 0.0005$, minimum cluster size of 5 voxels, lag 3. Notable sub-peaks within a larger region of activation follow the entry for the peak voxel, and are listed with an indent.

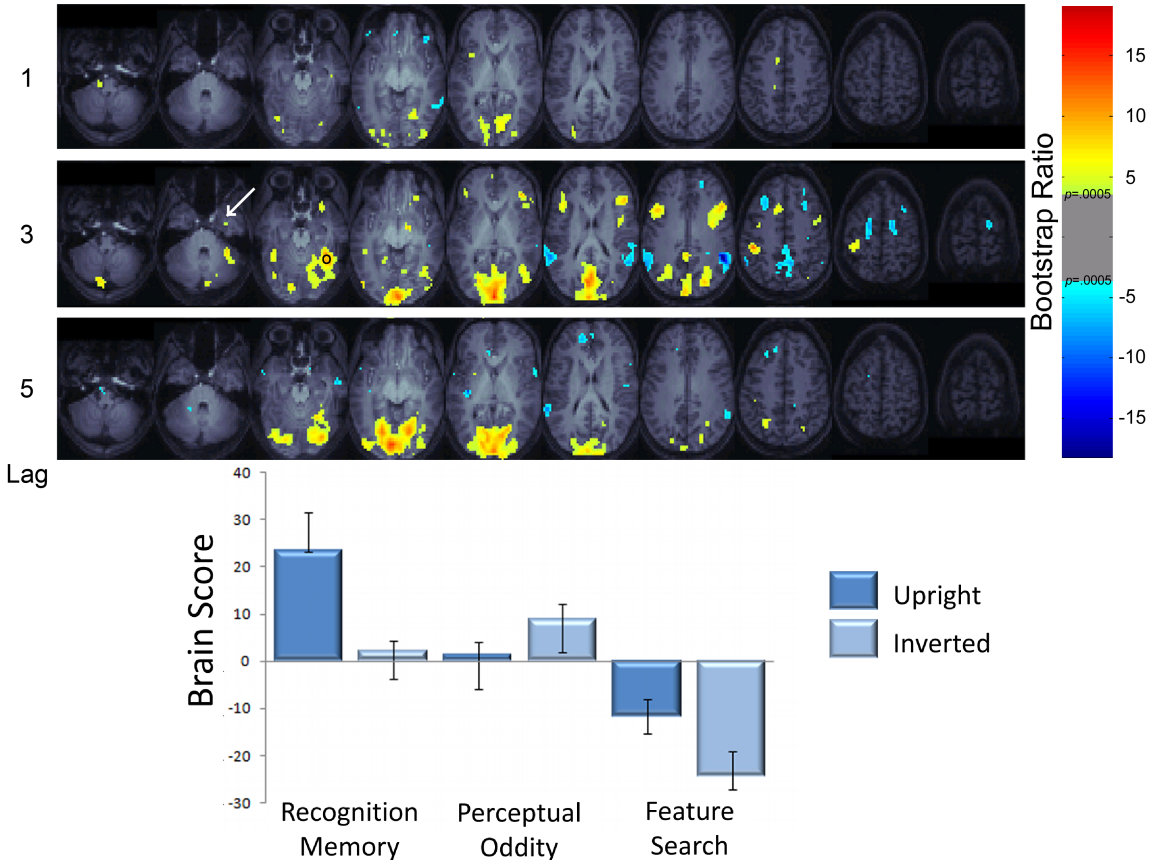

Figure 2.5. LV and associated saliences for PLS task contrast comparing the upright memory condition against all other experimental conditions. Lags 1–5 correspond to 2.5 s intervals encompassing the duration of the hemodynamic response within a trial. Error bars represent 95% confidence intervals derived by bootstrap estimation. White arrow at lag 3 indicates right PrC, black circle denotes peak of right FFA as determined by the univariate analysis of the localizer data.

Table 2.3.

Regions showing reliable saliences for the LV that contrasted the memory and oddity tasks vs. search and luminance tasks

Region	X	y	z	Bootstrap Ratio	Cluster Size (voxels)
	Talairach Coordinates				
Upright Memory > Experimental					
Cuneus	2	-91	1	12.61	2483
Fusiform Gyrus	35	-37	-20	9.26	
Amygdala	14	-4	-8	11.44	38
Inferior Parietal Lobule	-46	-31	40	8.72	155
Orbital Frontal Gyrus	38	35	4	8.50	523
Precuneus	20	-73	28	7.17	172
Middle Frontal Gyrus	-52	11	37	7.13	192
Middle Occipital Gyrus	-52	-73	-5	6.22	34
Medial Frontal Gyrus	-13	11	46	5.96	60
Angular Gyrus	-28	-58	34	5.50	108
Superior Temporal Sulcus	41	-58	7	5.28	90
Superior Frontal Gyrus	-4	62	1	5.27	68
Fusiform Gyrus	-40	-40	-17	5.08	38
PrC	29	20	-17	4.67	39
Parahippocampal Gyrus	-19	-46	-8	4.62	19
Inferior Frontal Gyrus	26	29	-5	4.38	20
Precentral Gyrus	-37	-4	40	4.28	17
Amygdala	-13	-1	-8	4.05	15
Experimental > Upright Memory					
Supramarginal Gyrus	50	-43	31	-10.22	291
Superior Temporal Gyrus	-61	-43	22	-7.56	242
Middle Frontal Gyrus	14	2	61	-7.23	124
Middle Frontal Gyrus	-16	-7	58	-6.77	110
Superior Frontal Gyrus	17	47	34	-6.04	125
Precuneus	8	-49	43	-5.35	124
Middle Frontal Gyrus	-28	26	43	-4.86	58

Note. Talairach coordinates indicate peak voxel. Bootstrap ratios all reflect minimum significance of $P < 0.0005$, minimum cluster size of 5 voxels, lag 3. Notable sub-peaks within a larger region of activation follow the entry for the peak voxel, and are listed with an indent.

2.4 Discussion

This study examined the impact of representational demands on involvement of PrC in face processing, manipulated at both the task and the stimulus level. Concerning task effects, right PrC showed increased responses in a recognition-memory and a perceptual-oddity task, as compared to a task of comparable difficulty that was designed to probe processing of an isolated face feature (feature-search). Effects of stimulus orientation in PrC were observed when the recognition-memory task for upright faces was compared with all other experimental conditions, including recognition memory for inverted faces. Notably, both effects in right PrC paralleled activity patterns in broader networks of regions that also included the right middle fusiform gyrus and the amygdala, regions that have previously been implicated in face processing in many other studies. As such, the current findings do not support the view that reference to a prior study episode clearly distinguishes the role of PrC from that of more posterior ventral visual pathway regions.

2.4.1 Task Effects in PrC

In the current study, we found clear support for the hypothesis that task demands modulate PrC response during face processing. In fact, PrC activity in the feature-search task for faces was more comparable to that in the luminance baseline task than that in the other experimental tasks that also involved presentation of faces. This finding suggests that PrC responses to face stimuli do not occur in a purely stimulus-driven manner. We note that the recognition-memory and oddity tasks required direct comparisons between multiple faces, while the search task could be performed in a sequential manner without invoking stimulus comparisons. Accordingly, the differential PrC response we observed across tasks is likely related to demands of face individuation that are necessary for such comparisons.

When interpreting the task effect in PrC it is important to keep in mind that the comparisons of faces for the recognition-memory and perceptual-oddity tasks required several seconds for completion. Several previous studies have reported a role for MTL structures, including PrC, in the maintenance of faces over short delays (Ranganath and

D'Esposito, 2001; Nichols et al., 2006; Olsen et al., 2009). Thus, PrC involvement in perceptual matching tasks, including the oddity judgments used here, may not only reflect the generation of an internal representation of the faces, but may also be related to maintenance of faces across the fixations needed for comparison and individuation [see Jeneson and Squire (2011) for related discussion]. Other studies that have previously linked PrC functions to face individuation include research in which activity has been observed during discrimination of faces that required generalization of identity across different viewpoints (Lee et al., 2008; Barense et al., 2010). Electrophysiological recording of cells in the anterior medial face patch of the rhesus monkey, which is situated in the anterior collateral sulcus, have also revealed cells with a high degree of invariance to head orientation in their responses (Freiwald and Tsao, 2010), a pattern that could reflect the presence of representations of face identity in this region. This interpretation would also be in line with prior findings from an fMRI study that examined the informational content of distributed face representations in the ventral visual pathway with multivariate pattern analyses (Nestor et al., 2011); it revealed that an anterior medial temporal region in, or in close proximity to PrC carried information about facial identity that allowed for classification of faces of four different individuals across different emotional expressions.

In another recent study, PrC activity was revealed during presentation of faces with high feature overlap (Mundy et al., 2012) even though the task only required participants to detect occasional extended stimulus presentation durations. This finding may appear to be in conflict with the interpretation we put forward for the current findings, as the experimental task used by Mundy et al. did not require discrimination of stimulus identity. It should be noted, however, that unlike the search for a subtle feature (“mole”) in the current study, the detection of infrequent “long” stimulus durations does little to orient the participant away from processing of face identity. Thus, differential involvement of PrC in perceptual tasks involving faces may only be revealed when such tasks are contrasted with conditions that preclude, or at least minimize, the processing of identity information.

2.4.2 Orientation Effects and the Role of Interference in PrC

With respect to the orientation manipulation, we only found partial support for our hypothesis; we did not reveal a pattern of PrC activity that directly mirrored the behavioral inversion effect across tasks. Instead, the recognition-memory task for upright faces was associated with increased activity in right PrC as compared to all other experimental conditions, including recognition of inverted faces. Findings from another recent study that addressed face-inversion effects also provide support for orientation sensitivity of PrC responses in the context of memory judgments (Nasr and Tootell, 2012). In that study, participants were presented with a series of face identities that varied in viewpoint from trial to trial. Participants performed a 1-back task in which they had to judge whether either the identity of a face or the location of a spot overlaid on the image was the same in consecutive trials. This latter task, like the feature-search task in the current study, had no demands for face individuation. A direct task comparison revealed activity in a number of regions with increases for the memory condition, including in the most anterior aspects of the collateral sulcus in PrC. Critically, inversion of the face stimuli reduced the size of this task effect in PrC.

From the perspective of a representational account of MTL functioning, it is perhaps surprising that we did not observe any evidence for an inversion effect in PrC during oddity judgments, even though task performance was affected by this manipulation. We note, however, that the orientation effect in PrC parallels to some extent our behavioral inversion effect, which was also larger in the recognition-memory than in the perceptual-oddity task. The differential sensitivity to inversion may be related to differences in the sensitivity of both tasks to interference from highly similar faces that were presented in other trials. It is well-documented in the neuropsychological literature on recognition memory that, due to increased interference, impairments associated with MTL damage become more pronounced with the lengthening of the list of to-be-remembered items (see Barense et al., 2012, for related arguments and findings); computational modeling of PrC functioning has shown that integrated representations can protect against such interference when it is the result of high degrees of feature overlap between items in the list (Cowell et al., 2006). In the context of the oddity task, revisiting

the faces in the display (i.e., refixations) during trial execution can provide a means to protect against such interference. In the memory task, by contrast, revisiting faces in the course of a trial will likely dilute subtle differences in familiarity between the target and lures due to neuronal adaptation. Accordingly, PrC contributions may be more critical. The essential role of PrC in supporting highly integrated representations for memory judgments is also supported by findings obtained with other stimulus classes in the recognition memory literature (see Yonelinas et al., 1999; Diana et al., 2008; Haskins et al., 2008); in this literature its role has been characterized as being critical for the "unitization" of stimulus features into objects.

2.4.3 Commonalities and Differences in the Role of the PrC and FFA in Face Processing

Multivariate PLS analyses showed that the response profile of PrC across our experimental manipulations mirrored that of other ventral visual pathway regions as well, including aspects of the fusiform gyrus that overlap with the FFA, and in the amygdala. Both structures have previously been shown to be differentially involved in the processing of faces (e.g., Rossion et al., 2012). Co-activation between these regions was revealed for the task effect relating to individuation and for the increase in activity for the upright memory trials as compared to all other experimental conditions. A common engagement of these regions across experimental manipulations hints that these regions provide critical input to PrC during face processing. Co-activation across select experimental manipulations, however, does not argue that the exact functional contributions of these regions are the same. Indeed, in a previous fMRI study conducted with the recognition-memory and oddity tasks for faces used here, we found differences in the FFA and PrC response related to the degree of similarity of the faces contained in each display (O'Neil et al., 2009). Specifically, PrC showed effects related to behavioral accuracy in both tasks even when the faces in the displays were highly similar. Accuracy effects observed in the FFA, by contrast, were limited to the condition of the oddity task in which the faces were least similar. This finding is in line with the idea that face representations in more posterior regions of the ventral visual pathway offer a more

limited resolution or fidelity than representations in PrC, and that the representations in PrC are more critical for individuation.

Some evidence for a posterior-anterior gradient in the nature of face representations that support individuation in the ventral visual pathway also comes from the fMRI study by Nestor and colleagues (2011) discussed previously. In that study, a multivoxel pattern analysis approach was used to reveal cortical regions that support classification of face identity across different facial expressions. Their analyses revealed four regions supporting classification of identity, including a region in the anterior collateral sulcus in right PrC and the right anterior fusiform gyrus (in the vicinity of the FFA). Examination of information content in these regions demonstrated a lower proportion of voxels in the most posterior fusiform region that carried identity information; however, there was no evidence for clear-cut differences between the right PrC region and the right anterior fusiform regions (in or close to the FFA). One possibility is that ventral visual pathway areas co-activate with PrC during online maintenance of information for the purpose of additional integration in the service of stimulus individuation. The quality of representations from earlier regions may initially be suboptimal to generate distinctive face representations for individuation at the level of PrC. Prolonged co-activation between PrC and regions of the ventral visual pathway may reflect iterative feedback mechanisms that further maximize the diagnostic information content of PrC representations.

2.4.4 Beyond Faces

Although numerous sources of evidence, reviewed above, point to a patch or area within PrC that appears to respond to face stimuli differentially, we do not mean to suggest that PrC as a whole, even in the right hemisphere, is a structure that is specialized for face processing only. Indeed, right-sided PrC involvement has been reported with various other stimulus classes in prior research (e.g., Henson et al., 1999; Buffalo et al., 2006; Litman et al., 2009). In the context of oddity tasks, for example, such involvement has been found in relation to matching of artificial objects ("greebles," Barense et al., 2010), animals, and artifacts (Devlin and Price, 2007) across viewpoints. Several studies have

also revealed right PrC involvement in recognition memory with stimuli other than faces (e.g., Montaldi et al., 2006; Staresina et al., 2011). Thus, the resilience to interference afforded by PrC-based representations may support discrimination across a broad range of stimuli, with different regions within PrC showing optimal tuning for specific stimulus classes.

2.5 References

Aguirre, G. K., Singh, R., & D'Esposito, M. (1999). Stimulus inversion and the responses of face and object-sensitive cortical areas. *Neuroreport*, *10*, 189-194.

Atkinson, A. P., & Adolphs, R. (2011). The neuropsychology of face perception: beyond simple dissociations and functional selectivity. *Philosophical Transactions of the Royal Society London, Series B: Biological Sciences*, *366*, 1726-1738. doi: 10.1098/rstb.2010.0349

Barense, M. D., Groen, I. I.A., Lee, A. C. H., Yeung, L-K., Brady, S. M., Gregori, M., Kapur, N., Bussey, T. J., Saksida, L. M., Henson, R. N. A. (2012). Intact memory for irrelevant information impairs perception in amnesia. *Neuron*, *75*, 157-167. doi: 0.1016/j.neuron.2012.05.014

Barense, M. D., Henson, R. N. A., Lee, A. C. H., & Graham, K. S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*, 389-401. doi: 10.1002/hipo.20641

Baxter, M. G. (2009). Involvement of Medial Temporal Lobe Structures in Memory and Perception. *Neuron*, *61*, 667-677. doi: 10.1016/j.neuron.2009.02.007

Brown, M. W., Warburton, E. C., & Aggleton, J. P. (2010). Recognition memory: Material, processes, and substrates. *Hippocampus*, *20*, 1228-1244. doi: 10.1002/hipo.20858

Buckley, M. J., & Gaffan, D. (2006). Perirhinal cortical contributions to object perception. *Trends in Cognitive Science*, *10*, 100-107. doi: 10.1016/j.tics.2006.01.008

Buffalo, E. A., Bellgowan, P. S. F., & Martin, A. (2006). Distinct roles for medial temporal lobe structures in memory for objects and their locations. *Learning & Memory*, *13*, 638-643. doi: 10.1101/lm.251906

Bussey, T. J., & Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus*, *17*, 898-908. doi: 10.1002/hipo.20320

Cate, A. D., Goodale, M. A., & Köhler, S. (2011). The role of apparent size in building- and object-specific regions of ventral visual cortex. *Brain Research*, *1388*, 109-122. doi: 10.1016/j.brainres.2011.02.022

Cate, A. D., & Köhler, S. (2006). The missing whole in perceptual models of perirhinal cortex. *Trends in Cognitive Science*, *10*, 396-397. doi: 10.1016/j.tics.2006.07.004

Chen, K., Reiman, E. M., Huan, Z., Caselli, R. J., Bandy, D., Ayutyanont, N., & Alexander, G. E. (2009). Linking functional and structural brain images with

multivariate network analyses: A novel application of the partial least square method. *NeuroImage*, *47*, 602-610. doi: 10.1016/j.neuroimage.2009.04.053

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *The Journal of Neuroscience*, *26*, 12186-12197. doi: 10.1523/JNEUROSCI.2818-06.2006

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010). Functional dissociations within the ventral object processing pathway: cognitive modules or a hierarchical continuum? *Journal of Cognitive Neuroscience*, *22*, 2460-2479. doi: 10.1162/jocn.2009.21373

Devlin, J. T., & Price, C. J. (2007). Perirhinal contributions to human visual perception. *Current Biology*, *17*, 1484-1488. doi: 10.1016/j.cub.2007.07.066

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2008). The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. *Journal of Experimental Psychology: Learning, Memory, & Cognition*, *34*, 730-740. doi: 10.1037/0278-7393.34.4.730

Epstein, R. A., Higgins, J. S., Parker, W., Aguirre, G. K., & Cooperman, S. (2006). Cortical correlates of face and scene inversion: a comparison. *Neuropsychologia*, *44*, 1145-1158. doi: 10.1016/j.neuropsychologia.2005.10.009

Farah, M. J., Wilson, K. D., Drain, M., & Tanaka, J. N. (1998). What is "special" about face perception? *Psychology Review*, *105*, 482-498.

Fox, C. J., Iaria, G., & Barton, J. (2008). Disconnection in prosopagnosia and face processing. *Cortex*, *44*, 996-1009. doi: 10.1016/j.cortex.2008.04.003

Freiwald, W. A., & Tsao, D. Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, *330*, 845-851. doi: 10.1126/science.1194908

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., & Turner, R. (1998). Event-related fMRI: characterizing differential responses. *NeuroImage*, *7*, 30-40.

Ganel, T., Gonzalez, C. L. R., Valyear, K. F., Culham, J. C., Goodale, M. A., & Köhler S. (2006). The relationship between fMRI adaptation and repetition priming. *NeuroImage*, *32*, 1432-1440. doi: 10.1016/j.neuroimage.2006.05.039

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J.C. (1999). Activation of the middle fusiform 'face area' increases with expertise in recognizing novel objects. *Nature Neuroscience*, 2, 568-573.

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia*, *45*, 32-41. doi: 10.1016/j.neuropsychologia.2006.04.015

Goh, W. D., & Lu, S. H. X. (2012). Testing the myth of the encoding-retrieval match. *Memory & Cognition*, *40*, 28-39. doi: 10.3758/s13421-011-0133-9

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*, 831-853. doi: 10.1016/j.neuropsychologia.2010.01.001

Haskins, A. L., Yonelinas, A. P., Quamme, J. R., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron*, *59*, 554-560. doi: 10.1016/j.neuron.2008.07.035

Haxby, J. V., Hoffman, E., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Science*, *4*, 223-233. doi: http://dx.doi.org/10.1016/S1364-6613(00)01482-0

Haxby, J. V., Ungerleider, L. G., Clark, V. P., Schouten, J. L., Hoffman, E. A., & Martin, A. (1999). The effect of face inversion on activity in human neural systems for face and object perception. *Neuron*, *22*, 189-199.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R.J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *The Journal of Neuroscience*, *19*, 3962-3972.

Ishai, A. (2008). Let's face it: it's a cortical network. *NeuroImage*, *40*, 415-419. doi: 10.1016/j.neuroimage.2007.10.040

James, T. W., Arcurio, L. R., & Gold, J. M. (2012). Inversion Effects in Face-selective Cortex with Combinations of Face Parts. *Journal of Cognitive Neuroscience*, *25*, 455-464. doi: 10.1162/jocn_a_00312

Jeneson, A., & Squire, L. R. (2011). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory*, *19*, 15-25. doi: 10.1101/lm.024018.111

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *Journal of Neurophysiology*, *100*, 129-139. doi: 10.1152/jn.00077.2008

Kanwisher, N., Tong, F., & Nakayama, K. (1998). The effect of face inversion on the human fusiform face area. *Cognition*, *68*, B1-B11.

Knutson, A. R., Hopkins, R. O., & Squire, L. R. (2012). Visual discrimination performance, memory, and medial temporal lobe function. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 13106-13111. doi: 10.1073/pnas.1208876109

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. *NeuroImage*, *56*, 455-475. doi: 10.1016/j.neuroimage.2010.07.034

Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H., Scahill, V. L., Gaffan, D., Bussey, T. J., Davies, R. R., Kapur, N., Hodges, J. R. and others. (2005). Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, *15*, 782-797. doi: 10.1002/hipo.20101

Lee, A. C. H., Scahill, V. L., & Graham, K. S. (2008). Activating the medial temporal lobe during oddity judgment for faces and scenes. *Cerebral Cortex*, *18*, 683-696. doi: 10.1093/cercor/bhm104

Lee, A. C. H., Yeung, L-K., & Barense, M. D. (2012). The hippocampus and visual perception. *Frontiers in Human Neuroscience*, *6*, 1-17. doi: 10.3389/fnhum.2012.00091

Leube, D. T., Yoon, H. W., Rapp, A., Erb, M., Grodd, W., Bartels, M., & Kircher, T. T. J. (2003). Brain regions sensitive to the face inversion effect: a functional magnetic resonance imaging study in humans. *Neuroscience Letters*, *342*, 143-146. doi: 10.1016/S0304-3940(03)00232-5

Litman, L., Awipi, T., & Davachi, L. (2009). Category-specificity in the human medial temporal lobe cortex. *Hippocampus*, *19*, 308-319. doi: 10.1002/hipo.20515

Marzi, T., & Viggiano, M. P. (2011). Temporal dynamics of face inversion at encoding and retrieval. *Clinical Neurophysiology*, *122*, 1360-1370. doi: 10.1016/j.clinph.2010.11.017

Maurer, D., Grand, R., & Mondloch, C. (2002). The many faces of configural processing. *Trends in Cognitive Science*, *6*, 255-260. doi: http://dx.doi.org/10.1016/S1364-6613(02)01903-4

McIntosh, A. R., Bookstein, F. L., Haxby, J, V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *NeuroImage*, *3*, 143-157.

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *NeuroImage*, *23*, 764-775. doi: 10.1016/j.neuroimage.2004.05.018

Milner, B., Squire, L. R., & Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron*, *20*, 445-468.

Moeller, S., Freiwald, W. A., & Tsao, D. Y. (2008). Patches with links: a unified system for processing faces in the macaque temporal lobe. *Science*, *320*, 1355-1359. doi: 10.1126/science.1157436

Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus*, *16*, 504-520. doi: 10.1002/hipo.20178

Mundy, M. E., Downing, P. E., & Graham, K. S. (2012). Extrastriate cortex and medial temporal lobe regions respond differentially to visual feature overlap within preferred stimulus category. *Neuropsychologia*, *50*, 3053-3061. doi: 10.1016/j.neuropsychologia.2012.07.006

Murray, E. A., & Bussey, T. J. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Science*, *3*, 142-151.

Murray, E. A., Bussey, T. J., & Saksida, L. M. (2007). Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. *Annual Review of Neuroscience*, *30*, 99-122. doi: 10.1146/annurev.neuro.29.051605.113046

Nairne, J. S. (2002). The myth of the encoding-retrieval match. *Memory*, *10*, 389-395. doi: 10.1080/09658210244000216

Nasr, S., & Tootell, R. B. H. (2012). Role of fusiform and anterior temporal cortical areas in facial recognition. *NeuroImage*, *63*, 1743-1753. doi: 10.1016/j.neuroimage.2012.08.031

Nestor, A., Plaut, D.C, & Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 9998-10003. doi: 10.1073/pnas.1102433108

Nichols, E. A., Kao, Y-C, Verfaellie, M., & Gabrieli, J. D. E. (2006). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus*, *16*, 604-616. doi: 10.1002/hipo.20190

Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J-B. (2005). Valid conjunction inference with the minimum statistic. *NeuroImage*, *25*, 653-660. doi: 10.1016/j.neuroimage.2004.12.005

O'Neil, E. B., Cate, A. D., & Köhler S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *The Journal of Neuroscience*, 29, 8329-8334. doi: 10.1523/JNEUROSCI.0374-09.2009

O'Neil, E. B., Protzner, A. B., McCormick, C., McLean, D. A., Poppenk, J., Cate, A. D., & Köhler, S. (2012). Distinct Patterns of Functional and Effective Connectivity between Perirhinal Cortex and Other Cortical Regions in Recognition Memory and Perceptual Discrimination. *Cerebral Cortex*, *22*, 74-85. doi: 10.1093/cercor/bhr075

Olsen, R. K., Nichols, E. A., Chen, J., Hunt, J. F., Glover, G. H., Gabrieli, J. D. E., & Wagner, A. D. (2009). Performance-related sustained and snticipatory sctivity in human medial temporal lobe during delayed match-to-sample. *The Journal of Neuroscience*, *29*, 11880-11890. doi: 10.1523/JNEUROSCI.2245-09.2009

Pinsk, M. A., DeSimone, K., Moore, T., Gross, C. G., & Kastner, S. (2005). Representations of faces and body parts in macaque temporal cortex: A functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 6996-7001. doi: 10.1073/pnas.0502605102

Poirier, M., Nairne, J. S., Morin, C., Zimmermann, F. G. S., Koutmeridou, K., & Fowler, J. (2012). Memory as discrimination: a challenge to the encoding-retrieval match principle. *Journal of Experimental Psychology: Learning, Memory, and Cognitive*, *38*, 16-29. doi: 10.1037/a0024956

Protzner, A. B., & McIntosh, A. R. (2009). Modulation of ventral prefrontal cortex functional connections reflects the interplay of cognitive processes and stimulus characteristics. *Cerebral Cortex*, *19*, 1042-1054. doi: 10.1093/cercor/bhn146

Pruessner, J., Köhler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani, N., Collins, D., & Evans, A. (2002). Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: Considering the variability of the collateral sulcus. *Cerebral Cortex*, *12*, 1342-1353. doi: 10.1093/cercor/12.12.1342

Rajimehr, R., Young, J. C., & Tootell, R. B. H. (2009). An anterior temporal face patch in human cortex, predicted by macaque maps. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 1995-2000. doi: 10.1073/pnas.0807304106

Ranganath, C., & D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron*, *31*, 865-873. doi: 10.1016/S0896-6273(01)00411-1

Rossion, B. (2009). Distinguishing the cause and consequence of face inversion: the perceptual field hypothesis. *Acta Psychologica*, *132*, 300-312. doi: 10.1016/j.actpsy.2009.08.002

Rossion, B., & Gauthier, I. (2002). How Does the Brain Process Upright and Inverted Faces? *Behavorial Cognitive Neuroscience Review*, *1*, 63-75. doi: 10.1177/1534582302001001004

Rossion, B., Hanseeuw, B., & Dricot, L. (2012). Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. *Brain and Cognition*, *79*, 138-157. doi: 10.1016/j.bandc.2012.01.001

Staresina, B.P., Duncan, K.D., & Davachi, L. (2011). Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related

event details. *The Journal of Neuroscience*, *31*, 8739–8747. doi: 10.1523/JNEUROSCI.4978-10.2011

Stevens, W. D., Hasher, L., Chiew, K. S., & Grady, C.L. (2008). A neural mechanism underlying memory failure in older adults. *Journal of Neuroscience*, *28*, 12820-12824. doi: 10.1523/JNEUROSCI.2622-08.2008

Suzuki, W. A., & Amaral, D. G. (1994). Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *Journal of Comparative Neurology*, *350*, 497-533.

Suzuki, W. A., & Baxter, M. G. (2009). Memory, Perception, and the Medial Temporal Lobe: A Synthesis of Opinions. *Neuron*, *61*, 678-679. doi: 10.1016/j.neuron.2009.02.009

Taylor, K. J., Henson R. N. A., & Graham, K. S. (2007). Recognition memory for faces and scenes in amnesia: dissociable roles of medial temporal lobe structures. *Neuropsychologia*, *45*, 2428-2438. doi: 10.1016/j.neuropsychologia.2007.04.004

Tsao, D. Y., Freiwald, W. A., Knutsen, T. A., Mandeville, J. B., & Tootell, R. B. H. (2003). Faces and objects in macaque cerebral cortex. *Nature of Neuroscience*, *6*, 989-995. doi: 10.1038/nn1111

Tsao, D. Y., Moeller, S., & Freiwald, W. A. (2008). Comparing face patch systems in macaques and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 19514-19519. doi: 10.1073/pnas.0809662105

Yin, R. K. (1969). Looking at upside-down faces. *Journal of Experimental Psychology*, *81*, 141-145.

Yonelinas, A. P., Kroll, N. E., Dobbins, I. G., & Soltani, M. (1999). Recognition memory for faces: when familiarity supports associative recognition judgments. *Psychological Bulletin Review*, *6*, 654-661.

Yovel, G., & Kanwisher, N. (2005). The neural basis of the behavioral face-inversion effect. *Current Biology*, *15*, 2256-2262. doi: 10.1016/j.cub.2005.10.072

Chapter 3

3 Resting-State fMRI Data in Humans Reveal Behaviorally-Relevant Connectivity Between the "Anterior Face Patch" in Perirhinal Cortex and the Fusiform Face Area

3.1 Introduction

The human brain is remarkably adept at the detection and individuation of faces in the environment. Studies examining the neural correlates of face perception and recognition in humans have revealed multiple brain regions that appear to play a specialized role in face processing (for review, see Gobbini and Haxby, 2007; Haxby et al., 2000; Ishai, 2008). In neuroimaging research, these regions are typically referred to as 'face-selective', based on their preferential, although not necessarily exclusive responses to faces as compared to other stimulus classes. The fusiform face area (FFA), the posterior region of the superior temporal sulcus (STS), and the occipital face area (OFA) in the ventral visual pathway have most commonly been found to exhibit such face-selectivity in studies that compared response to faces with those to other stimulus classes (Gobbini and Haxby, 2007; Haxby et al., 2000; Kanwisher and Yovel, 2006; Pitcher et al., 2011). Together, these three regions have been referred to as forming the 'core' face processing network. Other regions of the brain, in particular aspects of the anterior temporal lobe and amygdala (Amy), have also been implicated in many studies on face processing, although not necessarily with the same selectivity. They have been suggested to form an 'extended' face processing network. Regions in this extended network are thought to work in concert with the core regions, and are thought to guide behaviors relevant to social interaction, such as assessing mood, gauging the intentions of others, or accessing stored biographical information about people, when faces are encountered.

The investigation of face processing in macaques based on neurophysiological and neuroimaging techniques has also revealed face-selective patches of cortex with a

topographic arrangement that suggests some correspondence with the human face processing network. Curiously, the macaque face processing network has been shown to include an additional area of face selectivity in a ventral aspect of the anterior temporal lobe (Freiwald and Tsao, 2010; Moeller et al., 2008; Mur et al., 2010; Pinsk et al., 2009; Rajimehr et al., 2009; Tsao et al., 2003; Tsao et al., 2008) that was not reported in initial human investigations on face selectivity. In an attempt to resolve this disparity, more targeted analysis in humans has since uncovered an area on the medial surface of the temporal lobe, in the anterior collateral sulcus, that may be homologous to the anterior faces patch reported (with a more lateral location in monkey; Rajimehr et al., 2009); this regions falls within the anatomical boundaries of the perirhinal cortex (PrC) (Nasr and Tootell, 2012; O'Neil et al., 2009; see Insausti et al., 1998 for anatomical details). More recent investigations with functional localizer runs involving faces and other stimulus classes have reported differential activity for faces in the anterior collateral sulcus in the context of both a 1-back repetition task (Nasr and Tootell, 2012; Rajimehr et al., 2009; Rossion et al., 2012) as well as passive viewing paradigms (Rajimehr et al., 2009; Tsao et al., 2008).

With respect to the specific contributions of anterior temporal lobe regions to face processing, evidence in macaques has revealed identity-based face selectivity in anterior face-patch neurons (Freiwald and Tsao, 2010). Consistent with this finding, recent fMRI studies in humans indicate that a right anterior collateral sulcus region is more active when discriminating face images based upon their identity than based upon the position of a spot overlaid on the image (Nasr and Tootell, 2012; O'Neil et al., 2013). An examination of information content in fMRI data with multi-voxel pattern analyses (MVPA) has provided additional evidence to support a role of this region in individuation (Nestor et al., 2011). However, in this study it was reported that more posterior regions carry information about face identity as well. In addition, O'Neil et al. (2013), and Nasr et al. (2012) reported evidence in support of a degree of orientation specificity of anterior collateral sulcus responses in face recognition tasks. Employing a 1-back task, Nasr et al. compared activation levels for upright, inverted, and contrast-reversed faces. They found the greatest difference in activity for the upright as compared to the inverted face condition. In addition, an inversion effect was revealed in the right anterior collateral

sulcus (i.e., PrC) when O'Neil et al. (2013) compared activity associated with forced-choice recognition decisions for upright faces with several other discrimination tasks, including forced-choice recognition of inverted faces. PrC and the FFA were part of a pattern of brain regions exhibiting this effect, suggesting some joint sensitivity of the FFA and PrC to the face inversion manipulation.

In seminal neurophysiological work conducted in macaques, Moeller and colleagues (2008) demonstrated, using electrical stimulation combined with fMRI, that stimulation of face patches can reveal concomitant BOLD response in other face patches. This finding suggests that face patches in the macaque, including the anterior temporal face patch, are anatomically and functionally connected. Previous fMRI studies in humans have also examined the functional connectivity of face selective regions, however they have typically not assessed face-selective regions of the anterior temporal lobe (Turk-Browne et al., 2010; Zhang et al., 2009; Zhu et al., 2011, but see Avidan et al., 2013). Thus, a targeted examination of the extent to which face selective regions in PrC exhibit functional connectivity with the face network in the absence of face processing demands in humans has yet to be determined. Some insight into the ongoing functional interactions between PrC and the broader face-processing network in humans comes from a recent study by Avidan et al. (2013) that assessed functional connectivity during task and rest conditions in congenital prosopagnosics and age-matched controls. Functional connectivity between the anterior temporal face patch and the core face-processing network was reduced in congenital prosopagnosics during the viewing of faces, but not during rest. As Avidan et al. focused on the examination of reliable group differences, the extent to which aspects of PrC exhibits reliable connectivity with other regions supporting face processing in typically functioning individuals has yet to be quantified. Considered together, evidence from studies examining the monkey face patch system, human fMRI localizer studies, and congenital prosopagnosics suggest that aspects of right PrC may play a more integral role in the processing of faces than previously thought. While previously considered as part of the extended face-processing network, more recent converging evidence suggests that aspects of this region may be better conceptualized as supporting face representation more broadly. To assess the involvement of PrC in the face processing network, we examined resting-state

connectivity of core and extended face processing regions to probe the possibility that aspects of PrC may exhibit reliable, intrinsic connectivity with the face processing network, a finding that would be consistent with a more central role of PrC in face processing (Zhang et al., 2009).

In the current study, we employed a partial correlation approach to resting-state fMRI BOLD time-series to examine pair-wise connectivity of subject specific, face-selective regions of the face processing network. We examined areas of the 'core' face processing network, i.e. FFA, STS, and OFA, as well as regions identified as part of an extended face processing network, namely PrC and the Amy; these regions were recently identified in a large scale localizer study to exhibit face selectivity (Rossion et al., 2012). Motivated by the findings of Moeller et al. (2008), we predicted that concurrent involvement of FFA and PrC during face processing would be reflected in temporal synchronization of ongoing activity, even in the absence of face stimulus presentation. Critically, we sought to determine the extent to which this functional connectivity reflected activity in a face-specific network by controlling for non-specific fluctuations in another region exhibiting selectivity for a visual stimulus category (the parahippocampal place area). In addition, we clarified the nature of functional connectivity in the face processing network by examining resting-state activity with the added constraint that any connectivity between two regions was not common to other region(s) in the face processing network. This approach highlights specific coupling of signal between regions, revealing unique connectivity between specific nodes of the face processing network. Further, given our previous report of PrC and FFA sensitivity to an inversion manipulation for faces (stimulus inversion; O'Neil et al., 2013) we attempted to link FFA-PrC functional connectivity to participant's behavioral sensitivity to this manipulation.

3.2 Methods

Resting-state scans were collected during a session that included acquisition of experimental runs. The data from these experimental runs have been previously reported

(O'Neil et al., 2013). Twelve healthy right-handed university students (6 male, age range = 20-31 years) with normal or corrected-to-normal vision participated in this study. All participants gave written informed consent, and received compensation for their participation. This study received approval from the Health Sciences Research Ethics Board at the University of Western Ontario. Resting-state scans were collected during a session that included acquisition of other experimental runs. The data from these experimental runs have been reported previously (O'Neil et al., 2013). Participants from that study were included in the current examination if time constraints permitted collection of resting-state data (thirteen of sixteen participants from the original study). Three participants were not able to complete the resting-state scans due to time constraints, and one additional participant was excluded as face-selective aspects of right PrC failed to meet the threshold used for selection. Thus, analyses were completed on the sample of 12 remaining participants.

3.2.1 Resting-state and Functional Localizer Runs

Participants completed two resting-state scans. Participants were instructed to remain still, keep their eyes open, and to fixate on a white cross presented on a black background for the duration of the scan (6 minutes).

To identify regions contributing to the core and extended face processing networks, each participant also completed two functional-localizer runs (144 volumes each). These runs followed a protocol used successfully in several other studies from our lab (e.g., Cate et al., 2011; O'Neil et al., 2009) to elicit activation in the face processing network. Localizer runs involved presentation of grayscale faces, common objects, and places (buildings and landscapes) under passive viewing instructions. Stimuli from each category were presented in a blocked manner with alternating blocks of scrambled images corresponding to each stimulus category.

Additional task-related fMRI runs were also completed for a study reported elsewhere (O'Neil et al., 2013). While the fMRI data from these tasks was not considered in the context of the current study, the behavioral performance of participants was used to constrain our interpretation of the findings reported here.

3.2.2 MRI Acquisition

All MRI data were acquired on a 3-Tesla Siemens TIM MAGENTOM Trio scanner. T1-weighted anatomical images were obtained using an ADNI MPRAGE sequence [192 slices, time to repetition (TR) = 2300 ms, field of view (FOV) = 240 X 256 mm, matrix size = 240 X 256, flip angle = 9°, echo time (TE) = 4.25 ms, voxel size = 1 mm^3]. Functional MRI volumes were collected using a T2*-weighted single-shot gradient-echo-planar acquisition sequence [TR = 2500 ms, TE = 25 ms, slice thickness = 2.5 mm, in-plane resolution = 2.5 X 2.5 mm, FOV = 200 mm X 200 mm, matrix size 80 X 80 mm, flip angle = 60°]. Each functional volume included 49 contiguous slices. To optimize MR signal in the anterior temporal lobes, an oblique coronal orientation was selected, with an effort to prevent inclusion of the eyes in slices capturing this region. This slice plan provided full coverage of occipital and temporal lobes in all participants, with inferior aspects of frontopolar cortex, as well as the most superior aspects of parietal cortex not covered in some participants.

All preprocessing was implemented with the FMRIB Software Library toolbox (FSL; http://www.fmrib.ox.ac.uk) as well as custom Matlab code. Images were corrected for slice time differences (using Fourier-space time-series phase shifting), motion (6-parameter affine transformation), and intensity inhomogeneity. Images were then spatially smoothed [Gaussian kernel of full width at half-maximum = 5 mm]. Localizer scans were temporally high-pass filtered with a 100 s period and resting-state scans were band-pass filtered using a 2^{nd}-order Butterworth filter, ($0.009 < f < 0.08$; as in Fox et al., 2005). All images were then normalized [12-degrees of freedom linear affine transformation] to the standard 2 mm 152-brain MNI template. Global mean signal was not regressed out from the data because of its propensity for finding more anticorrelations (Murphy et al., 2009) and because it might remove physiologically important signals (Schölvinck et al., 2010).

Regions of interest were defined functionally, for each participant, using the localizer scans. A general linear model was specified for each localizer run with faces, places and objects as predictors. Scrambled images served as the baseline condition. Data were convolved using a double gamma hemodynamic response function. *Z*-maps

examining two contrasts, faces > places and places > faces, were generated for each run. Statistical maps were then combined at the subject level, resulting in a subject-specific fixed-effects contrast image for each of the two comparisons of interest. Resting-state analyses relied upon successful definition of every ROI in each participant from these independent functional localizer scans. Thus, we focused our analyses on the right hemisphere, which is known to exhibit a degree of specialization for faces (e.g., Bentin et al., 1996; Sergent et al., 1992) and indeed, showed more robust response to face stimuli during localizer runs than the corresponding regions in the left hemisphere. In addition, participants were excluded from the study only if the peak voxel activity of any region of interest failed to meet a minimum threshold $z = 1.64$. Note however, that at the group level, each functionally defined region of interest survived a mixed effects analysis at a false discovery rate (FDR)-corrected threshold of $p < .05$. As stated above, these criteria allowed all but one participant to be included in the analyses.

Examining the faces > places contrast, regions exhibiting a preferential response to face stimuli were defined using a 2mm sphere ROI centered on the peak voxel, separately for each participant, in the following regions: the FFA, located in the right middle fusiform gyrus, right PrC (constrained based upon the criteria of Pruessner et al., 2002), the right OFA in, or in the vicinity of the inferior occipital gyrus (Pitcher et al., 2011), the right (STS), and the right Amy. Confound regions (2 mm spheres) in the temporal stem adjacent to the right PrC, as well as anterior and posterior corpus callosum were defined for each participant based upon their structural scan (see Figure 3.1 for an representative subject's seed locations). Following ROI definition, the BOLD time-course from both runs were extracted from each subject-specific ROI, as well as from a ventricle mask derived from the standard 2 mm 152 brain MNI template.

To examine functional connectivity at rest across the core and extended face network regions, we used a partial correlation-based approach. For each participant, a matrix was constructed for each run containing the extracted BOLD time course of the ROIs described above, a ventricle mask derived from the 152 brain MNI template, as well as the six motion parameters of the respective scan. To reduce the likelihood that the

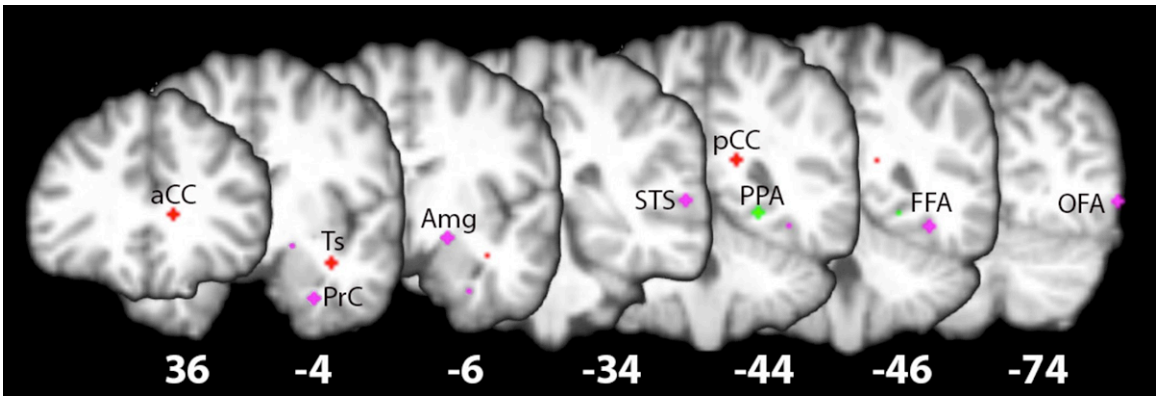

Figure 3.1. Seed regions from a representative participant. Numbers denote MNI coordinates of the Y-plane. aCC-Anterior corpus callosum, Ts-Temporal stem, PrC-Perirhinal cortex, Amg-Amygdala, STS-Superior temporal sulcus, pCC-Posterior corpus callosum, PPA-Parahippocampal place area, FFA-Fusiform face area, OFA-Occipital face area. Red and green colors denote white matter and grey matter control regions respectively, pink colors denote face processing regions.

partial correlations observed between face-selective regions might be driven by generic visual system activity propagated throughout the face recognition network, we adopted an approach forwarded by Turke-Browne and colleagues (2010); we partialled out activity in a control region sensitive to visually presented stimuli of another class, the scene-selective right parahippocampal place area (PPA) defined using the places > faces contrast in each participant). While it is not possible to account for all non-face specific activity through the inclusion of one or several control regions, the inclusion of the PPA ROI, and our other control ROIs (the white matter ROI adjacent to PrC in particular) takes advantage of a strength of the partial correlation approach to constrain our findings, as reliable correlations must capture variance unique across regions after accounting for the time courses of all confound measures. Partial correlations were then computed for each matrix, and a Fisher's *z* transformation was applied for the purpose of significance testing. Fisher *z*-transformed values were averaged across runs for each participant, and a 1-tailed *t*-test was used to assess if, across participants, this measure of functional connectivity was reliably different than 0 (i.e. the null hypothesis).

In addition, we expanded on Turke-Brown et al.'s (2010) approach whereby the activity of an additional region is partialled out in order to constrain connectivity findings. Specifically, we examined the extent to which connectivity between each pair of regions reflected a 'unique' partial correlation. To achieve this, we additionally partialled out activity in all other face selective ROI's when assessing resting-state connectivity in each possible pair of regions. This approach revealed resting-state connectivity between regions that was unique, i.e., not common to that between other regions in the face processing network.

3.3 Results

We assessed the connectivity of regions in the core and extended face processing networks in the absence of any explicit face processing demands. ROI time-courses extracted from the resting-state runs were used to generate a partial correlation matrix to examine the connectivity between subject-specific PrC, FFA, OFA, Amy, and STS (Figure 3.1). Nuisance covariates including ventricle, white matter, and motion time series as well as activity in the PPA were partialled out to account for non-neuronal and

non face-specific activity in the network, respectively. We first examined the extent to which the regions that comprise the core face processing network, identified based on our functional localizer scans, exhibited resting-state connectivity. Pair-wise partial correlations between the classically defined core face processing network revealed reliable resting-state connectivity between the OFA, FFA, and STS (FFA-STS $r = .19$, $p = .005$; FFA-OFA $r =. 35$ $p = .0001$; OFA-STS $r = .37$ $p = .04$). Next, we assessed the extent to which PrC and Amy exhibited resting-state connectivity with the rest of the core face processing network. Pair-wise partial correlations were revealed between the FFA, Amy and PrC, FFA-PrC $r = .09$, $p = .003$, FFA-Amy $r = .09$, $p < .014$ Amy-PrC $r = .18$ $p = .021$, whereby all other pair-wise partial correlations between regions were not reliably different that zero (Figure 3.2).

Demonstration of significant functional connectivity between PrC, Amy and FFA supports the notion that extended regions exhibit intrinsic connectivity with the face processing network. However, from this analysis it is not clear if the pattern of functional connectivity reflects unique connectivity between regions. For instance, partial correlations between PrC and Amy may reflect intrinsic functional connectivity between these regions, or alternatively, the common influence of a third source (i.e., FFA). To address this question, we examined the partial correlations between regions as before, but additionally controlling for the influence of each remaining face-selective ROI. Thus, significant functional connectivity between PrC and the Amy would reflect unique connectivity after accounting for shared covariance between non-face, anatomical ROIs, motion-related confounds, as well as the FFA, OFA, and STS. As can be seen in Figure 3.3, fewer regions exhibited resting-state connectivity that was independent of common variance in other face selective regions. Notably however, PrC exhibited unique functional connectivity with both the FFA ($r = .07$, $p = .007$) and Amy ($r = .18$, $p = .020$) after accounting for the influence of other face-selective regions. Unique connectivity was also revealed between FFA and OFA $r = .30$, $p = .0006$. This approach failed to reveal reliable connectivity between STS and the rest of the core face processing network (both FFA and OFA), a point we return to in the Discussion.

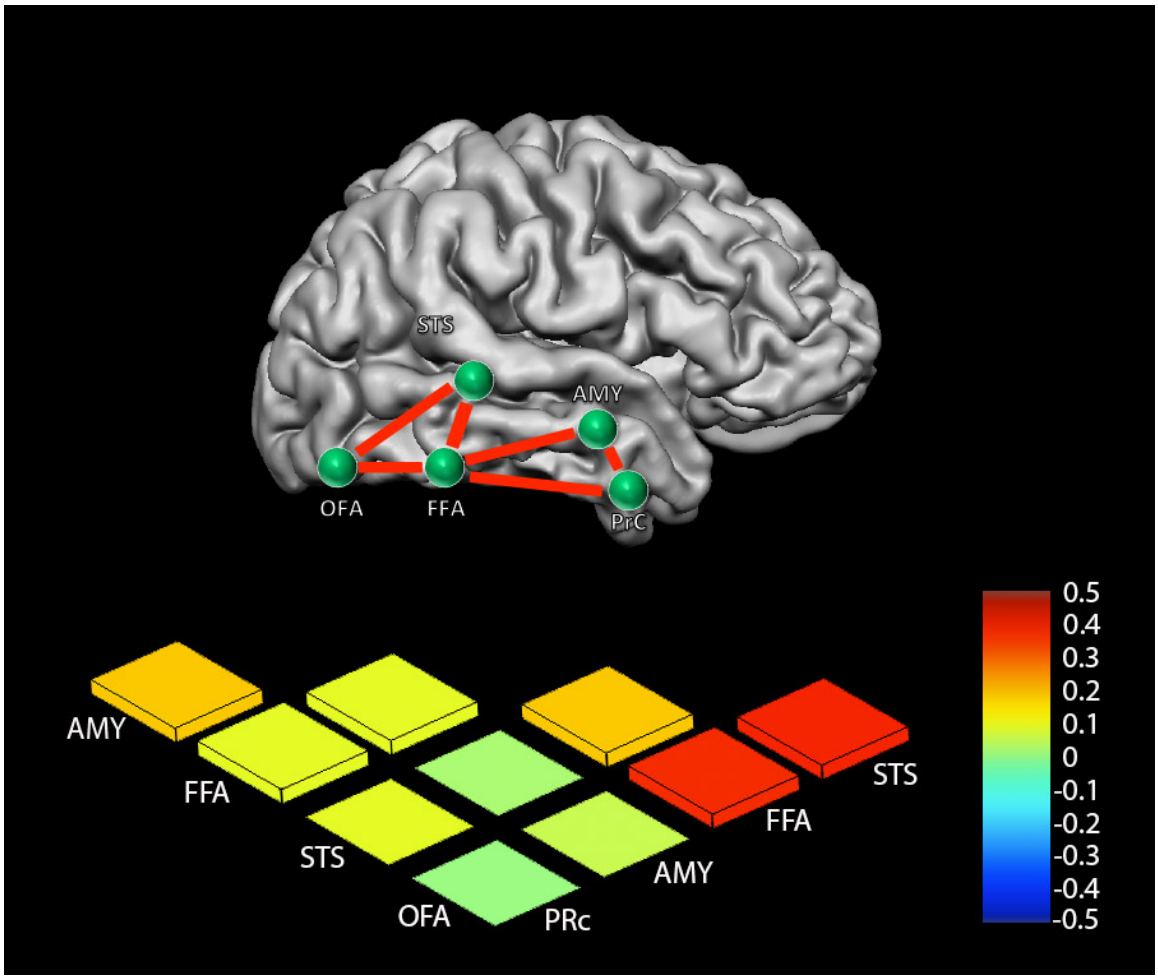

Figure 3.2. Partial correlations. Upper: Red bars denote reliable functional connectivity between face-selective regions, displayed as circular nodes on the surface of a rendered brain image for ease of visualization. Lower: Partial correlation matrix. Color scale reflects *z*-transformed *r*-values. Elevated cells denote correlations that were reliably different from zero.

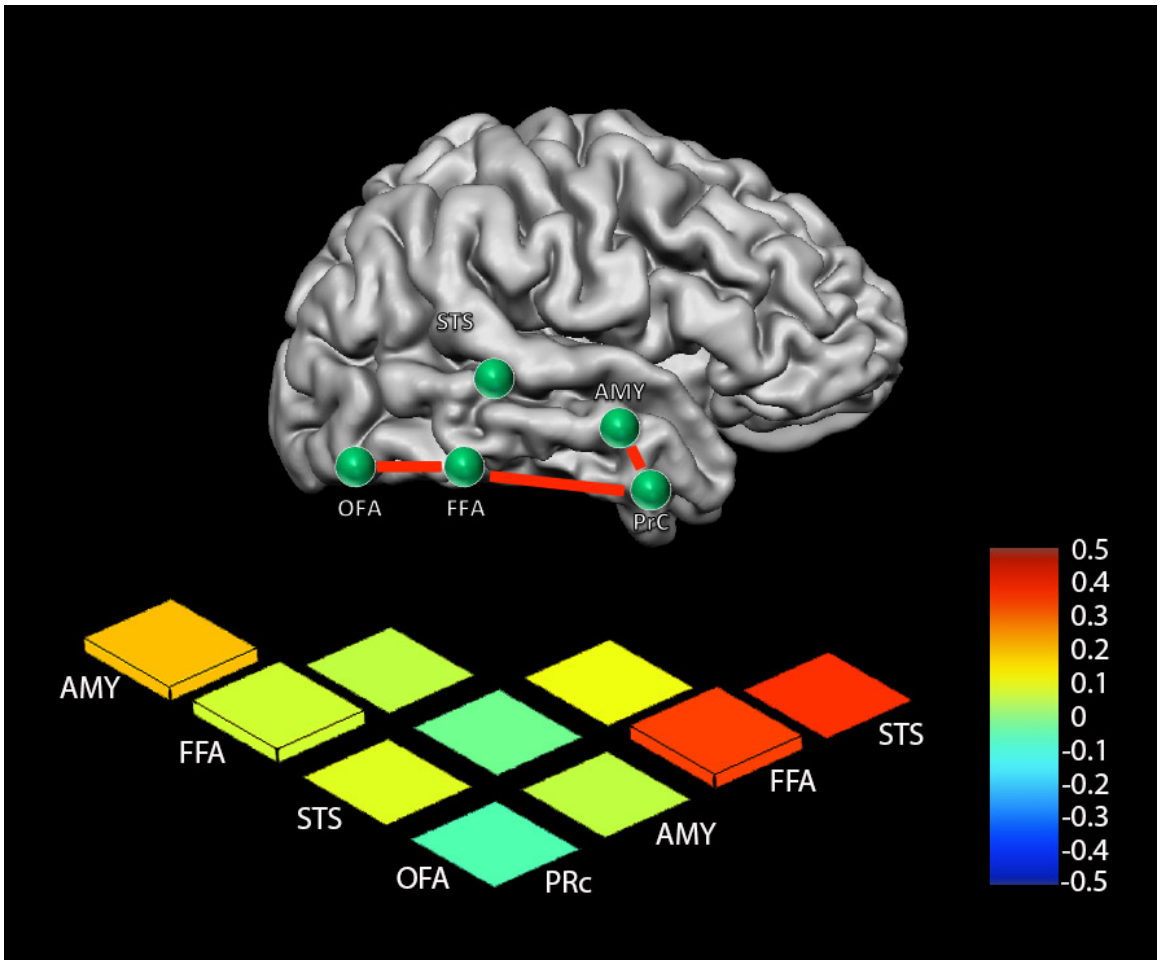

Figure 3.3. 'Unique' partial correlations. Upper: Red bars denote reliable functional connectivity between face-selective regions. Lower: Unique partial correlation matrix. Color scale reflects *z*-transformed *r*-values. Elevated cells denote correlations that were reliably different from zero. Note that unlike in Figure 3.2, each cell reflects the partialling out of activity from a distinct set of brain regions (due to the revolving nature of regions partialled from each analysis, i.e. all regions except for the pair being compared). Results are shown together in matrix form for ease of comparison.

Beyond evaluating the intrinsic coupling of face processing regions, we also investigated the relationship between connectivity measures and behavioral performance on an experimental face processing task based on data that were collected during the same experimental session, results of which have been published separately (O'Neil et al., 2013; Chapter 2). Our previous examination of these data focused on the effects of face inversion on recognition memory, visual oddity, and visual search tasks. The greatest behavioral effect of face inversion was present for the recognition memory task. Critically, aspects of right PrC and a fusiform region overlapping with the FFA were part of a pattern of brain regions affected by the inversion manipulation in this recognition memory task. Given this finding, we aimed to address in the current analyses whether unique connectivity in the face processing network during rest was related to the size of the behavioral inversion effect for the recognition memory task across participants. For each participant, we calculated the size of behavioral inversion effect (upright task accuracy – inverted task accuracy) for the memory task. We then examined the relationship between this behavioral marker of face processing and the strength of unique connectivity between our predefined face-selective regions (with other face processing areas partialled out). The analysis revealed PrC-FFA connectivity correlated with the strength of the behavioral inversion effect ($r = .73$, $p = .007$; Figure 3.4), with no other partial correlations relating to the behavioral inversion effect. In other words, the greater the functional connectivity strength between PrC and FFA, after accounting for influences in other regions, the greater the behavioral sensitivity to face inversion.

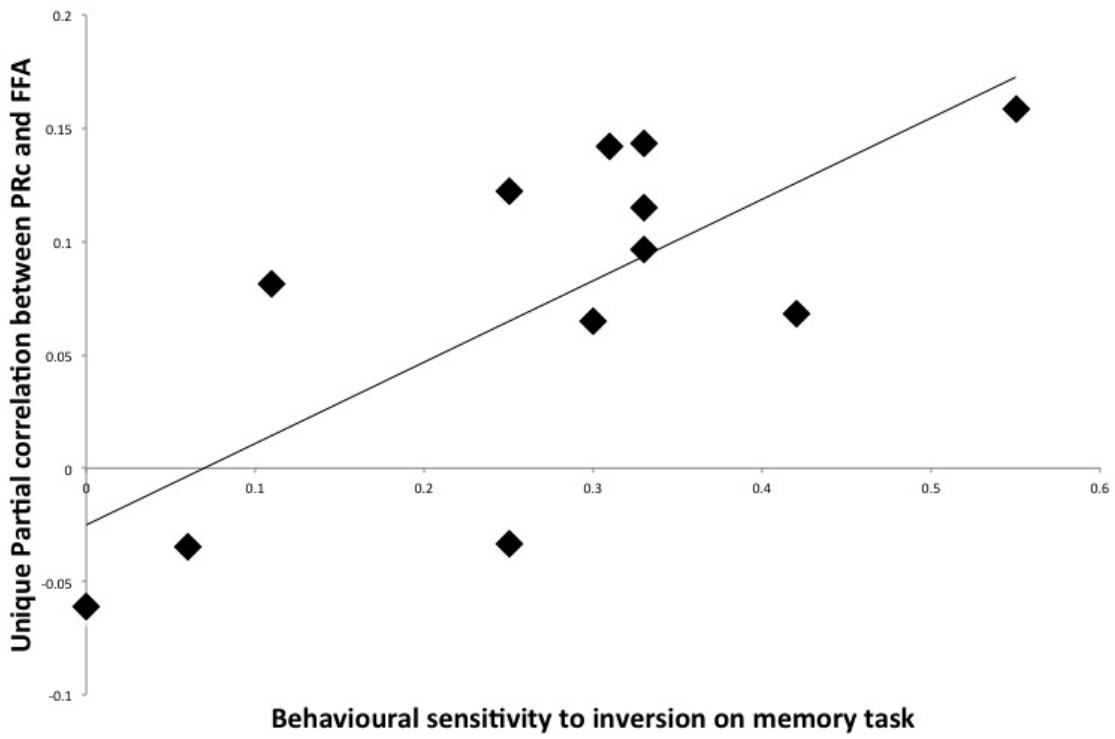

Figure 3.4. Scatterplot denoting the relationship between the unique partial correlation between PrC and FFA, and the sensitivity of participants to the inversion manipulation for the memory task. Each diamond represents a participant. Y-axis values denote the *z*-transformed *r*-values. X-axis values denote the size of the behavioral accuracy advantage for upright as compared to inverted faces.

3.4 Discussion

In the current study, we assessed the functional connectivity of the core and extended face processing network at rest, with a particular interest in aspects of right PrC that have previously been shown to have similar functional characteristics as the anterior temporal face patch in the macaque (Nasr and Tootell, 2012; Rajimehr et al., 2009; Rossion et al., 2012; Tsao et al., 2008; Von Der Heide et al., 2013). Face-selective regions were found to exhibit reliable, intrinsic connectivity, despite the absence of explicit face processing demands. Further, our findings suggest that face-selective voxels in PrC exhibit unique connectivity with the FFA that was not shared with other regions in the face processing network. This unique connectivity was correlated with variations in the behavioral effects of an orientation manipulation in a face recognition-memory task across participants, indicating that connectivity between PrC and FFA is behaviorally relevant.

FFA connectivity was common to all face-selective regions included in our correlation analyses, pointing to a possible hub-like role of the FFA. Nestor and colleagues (2011) have previously demonstrated a central functional role of an anterior fusiform region within the face processing network. These authors, using a multivariate analysis spotlight approach, uncovered four regions that support the representation of facial identity, including anterior fusiform cortex in the vicinity of FFA, and anterior temporal cortex, in or near PrC. Notably, the information content across these four regions with respect to face identity was similar, with the region exhibiting the greatest amount of mutual information, consistent with a hub-like role, located in the anterior region of the fusiform gyrus.

Expanding on Turke-Browne et al.'s (2010) approach, we also examined the 'unique' partial connectivity for each ROI pair by partialling out all additional face selective regions. As anticipated, given evidence that information content across the face processing network exhibits a degree of redundancy (Nestor et al., 2011), fewer pairwise partial correlations were significant after additionally controlling for activity across the remainder of the face selective regions. Notably, PrC was found to exhibit unique connectivity with both the Amy and FFA, findings that support a unique contribution of this region to the face processing network. On the other hand, both FFA-Amy and FFA-

STS connectivity were not found to be unique. This indicates that resting-state connectivity between these regions reflects, to some extent, activity partially redundant with that between other regions of the face processing network.

The importance of connectivity between the anterior temporal lobe and posterior regions has been suggested by findings from diffusion-based imaging approaches examining white matter pathways in the brain. The major white matter bundle connecting inferior visual regions such as the FFA and OFA with both the medial and lateral anterior temporal cortex is the inferior longitudinal fasciculus (Catani et al., 2003; Thomas et al., 2009). Evidence pointing to the behavioral relevance of this pathway for face processing comes from studies examining individuals with congenital prosopagnosia, i.e. a lifelong deficit in face processing. In contrast to the apparently normal functioning of the core face regions in these individuals, as assessed using task-based fMRI, investigations focusing on structural and functional connectivity of core face regions and the anterior temporal lobe have revealed distinctions between these individuals and normal control participants. Congenital prosopagnosics exhibit reduced white matter integrity of the inferior longitudinal fasciculus, and the extent of reduction is correlated with behavioral face recognition performance (Thomas et al., 2009). In addition, assessment of functional connectivity in individuals with congenital prosopagnosia during a 1-back task involving presentation of faces revealed reduced connectivity between the core face network and face-selective anterior temporal cortex as compared to controls (Avidan et al., 2013). These findings in congenital prosopagnosics suggest both a functional and structural dysfunction in the connectivity of anterior temporal and core face processing regions, and provide converging evidence for a prominent role of face-selective PrC in the behavioral discrimination of faces.

In typically functioning individuals, diffusion-based (diffusion spectrum imaging) assessment of the structural connectivity of face-selective regions of cortex has revealed connectivity between face-selective anterior temporal cortex and the FFA, as well as, to a lesser extent, the OFA (Pyles et al., 2013). Consistent with the current unique partial correlation findings in the current study, however, STS was not found to exhibit reliable connectivity with other regions of face-selective cortex, including the anterior temporal

face regions. Gschwind et al. (2012), using a different diffusion-based approach, also examined the nature of the structural connectivity of face-selective cortical regions. While they did not include the anterior temporal cortex, their analyses revealed high connectivity probability between the FFA and OFA, whereas the STS was not found to exhibit significant white matter connectivity with other face-selective regions, again suggesting a lack of direct connectivity between these two regions, as reported in the current study. The divergent findings regarding STS connectivity from our partial and "unique" partial correlation approaches are consistent with distinctions between the functional- and anatomical-connectivity literature: like Turke-Browne et al. (2010), we reveal connectivity between FFA and STS at rest, but the lack of unique connectivity between these two regions is consistent with the diffusion-based findings discussed above. It is possible that the partialling of activity in other face-selective regions may have eliminated a mediating influence on STS which gives rise to its resting-state connectivity, despite its apparent lack of direct connectivity with the rest of the face processing network. Thus, our findings suggest that correlated activity between these regions was also manifest elsewhere in the face processing network.

Demonstration of a behavioral correlation with connectivity between PrC and FFA suggests that resting-state connectivity, thought to be constrained by the underlying anatomical connectivity between regions (Greicius et al., 2009; Honey et al., 2009; Van Den Heuvel et al., 2009; Vincent et al., 2007; for review, see Damoiseaux and Greicius, 2009; Shen et al., 2012), can have consequences at the behavioral level (e.g., Hampson et al., 2006; Tambini et al., 2010). Previous research examining connectivity during tasks involving faces has demonstrated that stimulus- and task-related processing demands can modulate connectivity between these regions (e.g., O'Neil et al., 2011; see also Avidan et al., 2013). Resting-state connectivity likely reflects the occurrence of repeated functional interactions that occur over time. Increased strength of these interactions may support functional coupling during task conditions, aiding task performance. Insofar as resting-state connectivity reflects anatomical links between regions of the face processing network, correlations with behavior could also arise in the face processing network due to the influences of structural connectivity on the functional organization of the brain. A recent report has demonstrated that the location of the FFA can be predicted based upon

connectivity of other regions of the brain. Among these regions is a right anterior temporal region encompassing PrC (Saygin et al., 2012). Thus, PrC connectivity, together with connectivity of other regions may have a causal role in dictating the emergence of face-selectivity (i.e., the location of FFA) in the brain.

While the functional connectivity data presented here support a high degree of integration between aspects of PrC with FFA, we do not suggest that PrC as a whole, or even face selective subregions of PrC are necessarily exclusively dedicated to the processing of faces in humans. Right-sided PrC involvement has been reported with various other stimulus classes in prior research (e.g., Buffalo et al., 2006; Litman et al., 2009; Martin et al., 2013). The current study goes beyond previous investigations of the resting-state functional connectivity of PrC (Khan et al., 2008; Libby et al., 2012) by directly assessing the extent to which activity in PrC reflected activity in core and extended areas of the face processing network. Our findings point to an integration of PrC with the face processing network, in particular FFA, and support recent findings suggesting that STS may be anatomically distinct from the rest of the face processing network. Critically, these findings suggest a central role of the face selective region in PrC in the interplay between core and extended face networks.

3.5 References

Avidan, G., Tanzer, M., Hadj-Bouziane, F., Liu, N., Ungerleider, L.G., & Behrmann, M. (2013). Selective dissociation between core and extended regions of the face processing network in congenital prosopagnosia. *Cerebral Cortex*, *23*, 1-14. doi: 10.1093/cercor/bht007

Bentin, S., Allison, T., Puce, A., Perez, E., & Mccarthy, G. (1996). Electrophysiological studies of face perception in humans. *The Journal of Cognitive Neuroscience*, *8*, 551-565. doi: 10.1162/jocn.1996.8.6.551

Buffalo, E. A., Bellgowan, P. S. F., & Martin, A. (2006). Distinct roles for medial temporal lobe structures in memory for objects and their locations. *Learning & Memory*, *13*, 638-643. doi: 10.1101/lm.251906

Catani, M., Jones, D. K., Donato, R., & Ffytche, D. H. (2003). Occipito-temporal connections in the human brain. *Brain: A Journal of Neurology*, *126*, 2093-2107. doi: 10.1093/brain/awg203

Cate, A. D., Goodale, M. A., & Köhler S. (2011). The role of apparent size in building- and object-specific regions of ventral visual cortex. *Brain Research*, *1388*, 109-122. doi: 10.1016/j.brainres.2011.02.022

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function*, *213*, 525-533. doi: 10.1007/s00429-009-0208-6

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9673-9678. doi: 10.1073/pnas.0504136102

Freiwald, W. A., & Tsao, D. Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, *330*, 845-851. doi: 10.1126/science.1194908

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia*, *45*, 32-41. doi: 10.1016/j.neuropsychologia.2006.04.015

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*, 72-78. doi: 10.1093/cercor/bhn059

Gschwind, M., Pourtois, G., Schwartz, S., Van De Ville, D., & Vuilleumier, P. (2012). White-matter connectivity between face-responsive regions in the human brain. *Cerebral Cortex*, *22*, 1564-1576. doi: 10.1093/cercor/bhr226

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *The Journal of Neuroscience*, *26*, 13338-13343. doi: 10.1523/JNEUROSCI.3408-06.2006

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*, 223-233. doi: http://dx.doi.org/10.1016/S1364-6613(00)01482-0

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 2035-2040. doi: 10.1073/pnas.0811168106

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., Laakso, M. P., & Pitkänen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *American Journal of Neuroradiology*, *19*, 659-671.

Ishai, A. (2008). Let's face it: it's a cortical network. *NeuroImage*, *40*, 415-419. doi: 10.1016/j.neuroimage.2007.10.040

Kanwisher, N. G., & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical transactions of the Royal Society of London Series B, Biological Sciences*, *361*, 2109-2128. doi: 10.1098/rstb.2006.1934

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *Journal of Neurophysiology, 100*, 129–139. doi:10.1152/jn.00077.2008

Libby, L. A., Ekstrom, A. D., Ragland, J. D., & Ranganath, C. (2012). Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging. *The Journal of Neuroscience, 32,* 6550–6560. doi:10.1523/JNEUROSCI.3711-11.2012

Litman, L., Awipi, T., & Davachi, L. (2009). Category-specificity in the human medial temporal lobe cortex. *Hippocampus*, *19*, 308-319. doi: 10.1002/hipo.20515

Martin, C. B., McLean, D. A., O'Neil, E. B., & Köhler, S. (2013). Distinct familiarity-based response patterns for faces and buildings in perirhinal and parahippocampal cortex. *The Journal of Neuroscience*, *33*, 10915-10923. doi: 10.1523/JNEUROSCI.0126-13.2013

Moeller, S., Freiwald, W. A., & Tsao, D. Y. (2008). Patches with links: a unified system for processing faces in the macaque temporal lobe. *Science*, *320*, 1355-1359. doi: 10.1126/science.1157436

Mur, M., Ruff, D. A., Bodurka, J., Bandettini, P. A., & Kriegeskorte, N. (2010). Face-identity change activation outside the face system: "Release from adaptation" may not always indicate neuronal selectivity. *Cerebral Cortex*, *20*, 2027-2042. doi: 10.1093/cercor/bhp272

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage*, *44*, 893-905. doi: 10.1016/j.neuroimage.2008.09.036

Nasr, S., & Tootell, R. B. H. (2012). Role of fusiform and anterior temporal cortical areas in facial recognition. *NeuroImage*, *63*, 1743-1753. doi: http://dx.doi.org/10.1016/j.neuroimage.2012.08.031

Nestor, A., Plaut, D. C., & Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 9998-10003. doi: 10.1073/pnas.1102433108

O'Neil, E. B., Barkley, V. A., & Köhler, S. (2013). Representational demands modulate involvement of perirhinal cortex in face processing. *Hippocampus*, *23*, 592-605. doi: 10.1002/hipo.22117

O'Neil, E. B., Cate, A. D., & Köhler, S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *The Journal of Neuroscience*, *29*, 8329-8334. doi: 10.1523/JNEUROSCI.0374-09.2009

O'Neil, E. B., Protzner, A. B., McCormick, C., McLean, D. A., Poppenk, J., Cate, A. D., & Köhler, S. (2011). Distinct patterns of functional and effective connectivity between perirhinal cortex and other cortical regions in recognition memory and perceptual discrimination. *Cerebral Cortex*, *22*, 74-85. doi: 10.1093/cercor/bhr075

Pinsk, M. A., Arcaro, M., Weiner, K. S., Kalkus, J. F., Inati, S. J., Gross, C. G., Kastner, S. (2009). Neural representations of faces and body parts in macaque and human cortex: a comparative fMRI study. *Journal of Neurophysiology*, *101*, 2581-2600. doi: 10.1152/jn.91198.2008

Pitcher, D., Duchaine, B., Walsh, V., Yovel, G., & Kanwisher, N. (2011). The role of lateral occipital face and object areas in the face inversion effect. *Neuropsychologia*, *49*, 3448-3453. doi: 10.1016/j.neuropsychologia.2011.08.020

Pitcher, D., Walsh, V., & Duchaine, B. (2011). The role of the occipital face area in the cortical face perception network. *Experimental Brain Research*, *209*, 481-493. doi: 10.1007/s00221-011-2579-1

Pruessner, J., Köhler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani, N., Collins, D., & Evans, A. (2002). Volumetry of temporopolar, perirhinal,

entorhinal and parahippocampal cortex from high-resolution MR images: Considering the variability of the collateral sulcus. *Cerebral Cortex*, *12*, 1342-1353. doi: 10.1093/cercor/12.12.1342

Pyles, J. A., Verstynen, T. D., Schneider, W., & Tarr, M. J. (2013). Explicating the face perception network with white matter connectivity. *PLoS ONE*, *8*, e61611. doi: 10.1371/journal.pone.0061611

Rajimehr, R., Young, J. C., & Tootell, R. B. H. (2009). An anterior temporal face patch in human cortex, predicted by macaque maps. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 1995-2000. doi: 10.1073/pnas.0807304106

Rossion, B., Hanseeuw, B., & Dricot, L. (2012). Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. *Brain and Cognition, 79*, 138-157. doi: 10.1016/j.bandc.2012.01.001

Saygin, Z. M., Osher, D. E., Koldewyn, K., Reynolds, G., Gabrieli, J. D. E., & Saxe, R. R. (2012). Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. *Nature Neuroscience*, *15*, 321-327. doi: 10.1038/nn.3001

Schölvinck, M. L., Maier, A., Ye, F. Q., Duyn, J. H., & Leopold, D. A. (2010). Neural basis of global resting-state fMRI activity. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 10238-10243. doi: 10.1073/pnas.0913110107

Sergent, J., Ohta, S., & MacDonald, B. (1992). Functional neuroanatomy of face and object processing. A positron emission tomography study. *Brain: A Journal of Neurology*, *115*, 15-36. doi: 10.1093/brain/115.1.15

Shen, K., Bezgin, G., Matthew Hutchison, R., Gati, J. S., Menon, R. S., Everling, S., & McIntosh, A. R. (2012). Information processing architecture of functionally defined clusters in the macaque cortex. *The Journal of Neuroscience*, *32*, 17465-17476. doi: 10.1523/JNEUROSCI.2709-12.2012

Tambini, A., Ketz, N., & Davachi, L. (2010). Enhanced brain correlations during rest are related to memory for recent experiences. *Neuron*, *65*, 280-290. doi: 10.1016/j.neuron.2010.01.001

Thomas, C., Avidan, G., Humphreys, K., Jung, K. J., Gao, F., & Behrmann, M. (2009). Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nature Neuroscience*, *12*, 29-31. doi: 10.1038/nn.2224

Tsao, D. Y., Freiwald, W. A., Knutsen, T. A., Mandeville, J. B., & Tootell, R. B. H. (2003). Faces and objects in macaque cerebral cortex. *Nature Neuroscience*, *6*, 989-995. doi: 10.1038/nn1111

Tsao, D. Y., Moeller, S., & Freiwald, W. A. (2008). Comparing face patch systems in macaques and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 19514-19519. doi: 10.1073/pnas.0809662105

Turk-Browne, N. B., Norman-Haignere, S. V., & Mccarthy, G. (2010). Face-specific resting functional connectivity between the fusiform gyrus and posterior superior temporal sulcus. *Frontiers in Human Neuroscience*, *4*, 1-15. doi: 10.3389/fnhum.2010.00176

Van Den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*, *30*, 3127-3141. doi: 10.1002/hbm.20737

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., Zempel, J. M., Snyder, L. H., Corbetta, M., & Raichle, M. E. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, *447*, 83-86. doi: 10.1038/nature05758

Zhang, H., Tian, J., Liu, J., Li, J., & Lee, K. (2009). Intrinsically organized network for face perception during the resting state. *Neuroscience Letters*, *454*, 1-5. doi: 10.1016/j.neulet.2009.02.054

Zhu, Q., Zhang, J., Luo, Y. L. L., Dilks, D. D., & Liu, J. (2011). Resting-state neural activity across face-selective cortical regions is behaviorally relevant. *The Journal of Neuroscience*, *31*, 10323-10330. doi: 10.1523/JNEUROSCI.0873-11.2011

Chapter 4

4 Distinct Patterns of Functional and Effective Connectivity between Perirhinal Cortex and Other Cortical Regions in Recognition Memory and Perceptual Discrimination[2]

4.1 Introduction

Mechanisms that allow the human brain to create internal representations of objects are fundamental to both memory and perception. For example, in order to recollect an encounter with a previously viewed object successfully, a stored representation of that object must contain sufficient detail so as to avoid confusion with encounters of other similar objects. Likewise, discriminating between similar objects currently in view requires the development of sufficiently detailed internal representations to allow for their differentiation. An important issue of current interest in cognitive neuroscience is whether structures in the medial temporal lobe (MTL), specifically perirhinal cortex (PrC), which interfaces the MTL with the ventral visual pathway, support representations of objects that are critical for perceptual as well as for memory-based discriminations (Baxter, 2009; Suzuki, 2009).

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According to the prevailing view of brain organization, the MTLs act as an integrated modular system that is dedicated to declarative memory (Squire et al., 2004). This memory system is thought to maintain sharp neuroanatomical and functional boundaries with perceptual systems, including lateral and inferior temporal lobe structures that are dedicated to visual object identification, that is, the ventral visual pathway (e.g., Suzuki, 2010). MTL mechanisms, including those in PrC, are thought to be critical only for recognition memory, that is, recognition of the prior occurrence of an object after a delay but not for online discrimination of simultaneously presented objects in visual perceptual tasks. This standard view has recently been put into question by several reports of visuoperceptual deficits in association with PrC damage in human and nonhuman primates (Eacott et al., 1994; Buckley and Gaffan, 1997; Bussey et al., 2002; Bussey et al., 2003; Barense et al., 2005; Lee et al., 2005; Lee et al., 2006; for review, see Buckley and Gaffan 2006; Murray et al., 2007). Studies examining the effects of PrC lesions in nonhuman primates have revealed impairments in a number of tasks that lack an obvious long-term declarative memory component. For example, Buckley et al. (2001) reported that monkeys with PrC lesions were impaired when required to determine the "odd" stimulus from a visual array of simultaneously presented similar objects. These deficits were related the degree of visual similarity between the foil stimuli and the target. Similarly, studies of humans with large MTL lesions that include PrC have uncovered impairments in visual oddity or oddball discrimination tasks when discriminanda are highly similar (Lee et al., 2005, Lee et al., 2006; cf., Shrager et al., 2006). Functional neuroimaging research in healthy participants also supports a role of PrC in oddity or oddball judgments and other perceptual discriminations (Devlin and Price 2007; Lee et al., 2007; O'Neil et al., 2009; Barense et al., 2010).

Although the evidence in support of a role of the MTL in functions beyond declarative memory remains controversial, it has inspired promising alternate theoretical accounts that reject the notion that the MTL acts as a unified, specialized declarative memory system. A radically different proposal is that different MTL structures may be specialized for distinct computations that are tied to the representation of unique classes of stimuli or experiences (Murray et al., 2007; Graham et al., 2010). Within such a framework, PrC has been proposed to constitute an extension of the representational

hierarchy within the ventral visual pathway for object identification; it is thought to be recruited in tasks, perceptual or mnemonic, that require discriminations of objects with highly overlapping features. It has been proposed that PrC may provide a representation of the conjunctions of features (Murray and Bussey, 1999; Murray et al., 2007) or of gestalt-characteristics (Cate and Köhler, 2006) that are critical when individual perceptual features are insufficient for unique object identification. Computational modeling has demonstrated that such integrated higher-order representations are particularly important for recognition of prior occurrence of objects following delays. A typical delay is filled with a constant stream of visual input that creates massive interference at the feature level. Highly integrated object representations supported by PrC would allow for resolution of this interference in the assessment of the familiarity of a specific object at the time of its reoccurrence (Cowell et al., 2006, Cowell et al., 2010). Complementing the role of PrC, hippocampal contributions would allow for representations that contain contextual information pertaining to a specific object encounter (e.g.,Eichenbaum et al., 2007).

We recently reported a functional magnetic resonance imaging (fMRI) study whose findings argue against the classic view of MTL specialization for declarative memory and provide support for the representational account of PrC functioning just discussed (O'Neil et al., 2009). Using morphed faces as stimuli, we compared PrC activity while subjects completed 2 forced-choice tasks, both involving the presentation of 3 highly similar faces. An oddball task required the selection of a face most different from the others in the display, while a recognition memory task required the selection of the item presented in an earlier study phase. A luminance judgment task served as a baseline task of comparable difficulty that did not require referencing the type of complex stimulus representations that PrC is proposed to support. When contrasted with the baseline task, both experimental tasks engaged right PrC to an equivalent degree. Critically, PrC activity was also found to be greater for accurate than inaccurate trials in both tasks. While these findings clearly suggest common PrC involvement in recognition memory and perceptual discrimination, they also raise interesting new questions.

Clearly, tasks that require discrimination of multiple stimuli based on either mnemonic or perceptual information still have processing demands that are distinct from each other, even when the level of representational detail and integration required is considered comparable. Most importantly, recognition memory requires explicit assessment of a memory–strength signal associated with a stimulus currently in view or the recovery of contextual information from a prior related encounter, whereas perceptual discrimination does not. Performing these different tasks also evokes distinct phenomenological experiences; participants typically do not confuse whether their judgment is perceptual or mnemonic in nature. This situation raises the question as to what brain mechanisms differ between recognition memory and perceptual discrimination when PrC is commonly involved. Resolution of this question cannot be achieved by examining the representational role of PrC in isolation. Instead, broader processing dynamics related to processes of integration must be considered at the network level (McIntosh, 1999; Friston, 2002). Here, we took such an approach and revisited the fMRI data we reported previously (O'Neil et al., 2009) in order to examine whether the functional and effective connectivity of PrC with other cortical regions differed between the perceptual and recognition memory tasks that revealed common PrC involvement.

It is widely agreed that access to and manipulation of representations recovered through MTL mechanisms depends on control processes supported by prefrontal cortex (PFC; for a discussion, see Moscovitch 1992; Simons and Spiers 2003). Generally speaking, control processes shape the goal of any such attempt, the elaboration of the cue provided (if any), and the monitoring of the outcome of search processes. Functional neuroimaging research has provided considerable evidence that implicates PFC together with MTL structures in declarative memory, including at retrieval in recognition memory tasks (Skinner and Fernandes 2007; Mitchell and Johnson 2009). However, while many efforts have focused on parsing their distinct roles, the direct examination of functional interactions between the MTL and PFC has received much less attention so far (but see Köhler et al., 1998; Habib et al., 2003; McIntosh et al., 2003; Ranganath et al., 2005; Axmacher et al., 2008; McCormick et al., 2010). Thus, at present, it remains unclear whether such functional interactions differ between memory and perceptual tasks

that engage PrC equally. Given that PFC has also been implicated in control processes supporting visual attention tasks and perceptual decision making (Desimone and Duncan, 1995; Miller and Cohen, 2001; Heekeren et al., 2008), it would be over simplistic to assume that functional interactions between PrC and PFC are simply absent when participants engage in perceptual discriminations. Instead, the unique processing demands that are associated with recognition decisions and perceptual discriminations are more likely reflected in distinct patterns of interaction involving different PFC regions as well as additional posterior cortical structures.

Past fMRI studies have revealed the involvement of a number of different PFC regions in recognition memory. Left frontopolar and dorsolateral PFC regions have been found to be engaged most consistently when participants aim to recollect contextual detail about a prior encounter with the stimulus at hand (e.g., Henson et al., 1999; Rugg et al., 1999; Cansino et al., 2002; Dobbins et al., 2002; Dobbins and Wagner, 2005). By contrast, right dorsolateral and ventrolateral PFC regions have more frequently been involved in familiarity-based recognition in the absence of a requirement for contextual recovery (Henson et al., 1999; Dudukovic and Wagner, 2007). Involvement of ventrolateral PFC regions has also been linked to the evaluation of perceptual information when it is required for stimulus-based or contextually based recognition (Kostopoulos and Petrides, 2003; Dobbins and Wagner, 2005). That such an involvement might be more pronounced in memory processing is suggested by findings showing that midventrolateral PFC is differentially associated with mnemonic intentions when complex perceptual stimuli are being viewed (Dove et al., 2006). Based on these findings, we expected that aspects of right ventrolateral PFC would be part of the pattern of cortical regions that show differential coupling with PrC in the forced-choice recognition task and the perceptual oddball task for faces that we used previously. Other cortical regions that might show such differential interactions with PrC are midline structures in posterior cingulate and retrosplenial cortex; these structures have frequently been implicated in recognition memory in prior fMRI research (e.g., Henson et al., 1999; Daselaar et al., 2006; for review, see Wagner et al., 2005; Skinner and Fernandes, 2007; Vann et al., 2009) and have been reported to show an increase in activity for recognition memory as compared with visual attention tasks (e.g., Cabeza et al., 2003).

The latter finding has led to the suggestion that posterior midline structures could be involved in orienting attention to internally generated representations.

We also expected that some cortical regions would show a comparable functional coupling with PrC in recognition memory and perceptual discrimination, including aspects of PFC. A growing number of fMRI findings suggests that some of the control processes supported by PFC, in particular by dorsolateral PFC, in declarative memory tasks may not be unique to the domain of episodic memory (Cabeza et al., 2003; Dobbins and Han, 2006; Marklund et al., 2007; Han et al., 2009; Hayama and Rugg, 2009; for review, see Naghavi and Nyberg, 2005). One prominent idea in the literature is that dorsolateral PFC involvement may be linked to selective visual attention demands that are critical for task performance in many domains (e.g., Cabeza et al., 2003; Mayer et al., 2007). In the current experimental paradigm, for example, such demands would relate to the fact that all experimental trials required processing of multiple simultaneously presented faces and the selection of only one of them as the target for responding.

To examine functional connectivity of PrC, we employed seed-based multivariate partial least square (PLS) analyses in the current investigation (McIntosh et al., 1996; McIntosh et al., 2004). This method allowed us to assess task-related commonalities and differences in patterns of correlation between activity in PrC and the rest of the brain. In a second analysis, we employed structural equation modeling (SEM) to examine changes in effective connectivity across our 2 tasks for a subset of those regions identified with seed PLS. We performed this analysis to help constrain the interpretation of the PLS findings based on direct consideration of neuroanatomical connectivity in a simplified network model (for rationale, see Mclntosh and Gonzalez-Lima, 1994; Protzner and McIntosh, 2006). Specifically, we aimed to determine whether within such a model task-related differences in functional interactions would emerge for regions known to be directly connected with PrC.

4.2 Materials and Methods

A detailed description of the experimental design and scanning protocol has been presented previously (O'Neil et al., 2009). Thus, only a summary will be provided, in addition to the specific aspects that pertain to the new fMRI analyses presented here.

4.2.1 Participants

Eighteen right-handed healthy individuals, each with normal or corrected-to-normal vision, participated in this study. Each received compensation for their participation. This study received approval from the Health Sciences Research Ethics Board of the University of Western Ontario.

4.2.2 Materials and Procedures

The fMRI study consisted of 2 experimental tasks and a baseline task, intermixed in a fast event-related design. All tasks required the selection of 1 of 3 simultaneously presented visual items; subjects made their selections using an MR-safe keypad. Stimuli for each trial of the experimental tasks were created by morphing a pair of color face photographs of Caucasian individuals with neutral expressions. The original faces of each pair served as endpoints of a continuum on which 3 morphed faces were captured. To create the targets for the perceptual oddball task, 1 of 3 faces was captured at a disproportionate distance to the other two along the morph continuum. Stimuli that composed a memory trial were created in a similar way. However, images were captured at points equally spaced on the morph continuum such that there was no perceptually defined oddball item. Stimuli that served as targets for memory trials were studied in a prescan study session. Memory task difficulty was modulated by manipulating repetition at study exposure (1 or 3 times). Oddball task difficulty was manipulated by changing the degree to which the oddball target was disproportionately positioned along the morph continuum. The baseline task involved presentation of 3 semitransparent white squares of varying luminance overlaid on a visual noise background. On each trial, 1 of the 3 squares possessed 5% greater luminance than the other 2 squares. The baseline task required the

selection of the item with the greatest luminance. All experimental stimuli were trial unique.

All participants completed 6 experimental runs, each with 36 trials including all trial types (see Fig. 4.1*A*). Before each run, the 12 face images that served as targets for the memory task were presented for memorization for 3000 ms each, with a 1000 ms intertrial interval. During scanning, every trial started with presentation of an alphanumeric cue for 1000 ms, which indicated the type of upcoming task (memory, perception, or baseline), followed by a display of 3 critical stimuli for 5000 ms. Participants were required to choose the target item (i.e., studied, oddball, or brightest, respectively) while the stimuli remained on screen. Fixation period between trials was jittered. Trial order and jitter length were determined using Optseq2 (Dale 1999).

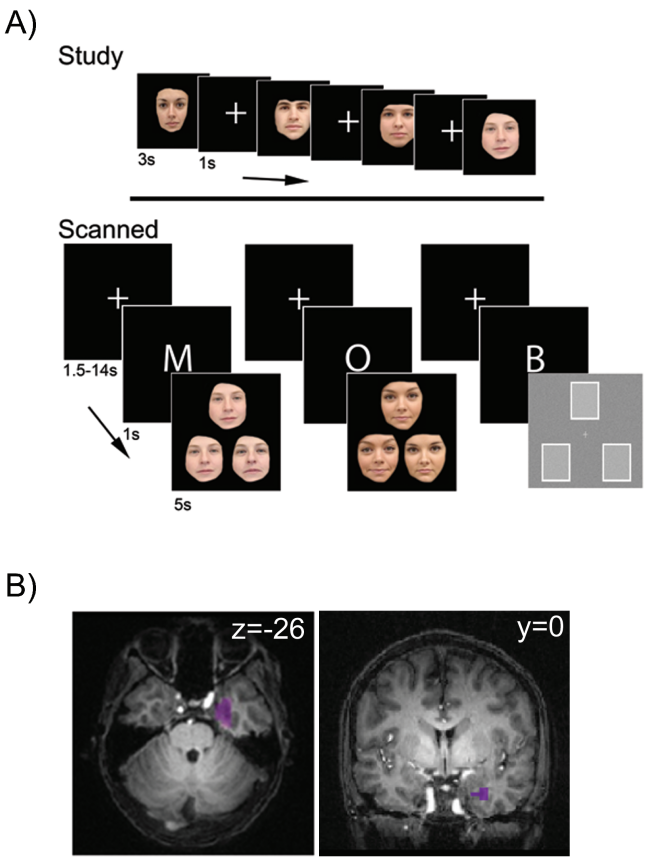

Figure 4.1. A) Experimental design. Prior to scanning, participants studied a series of faces. During scanning individuals performed 3 different types of judgments. M = forced-choice recognition memory task; O = perceptual oddball task; B = luminance baseline task. (B) PrC seed region on transverse and coronal slices of structural MR image in representative participant.

4.2.3 Summary of Behavioral Results

To briefly summarize the previously reported behavioral results (O'Neil et al., 2009), the mean behavioral accuracy (measured as percent correct ± standard error of the mean) for difficult and easy memory conditions was 54.60 ± 2.72 and 66.08 ± 2.80, respectively. The mean accuracy for the difficult and easy perceptual oddball conditions was 50.45 ± 1.98 and 72.90 ± 1.85, respectively. Critically, behavioral performance for the difficult condition of both experimental tasks, as well as overall performance when collapsed across difficulty, was matched in terms of accuracy (*t*-tests; all *P*s > 0.10). In addition, accuracy for the luminance baseline task (59.23 ± 5.00) did not differ from that of either of these 2 conditions.

4.2.4 Scanning Protocol

Scanning was completed on a 4-T whole body scanner (Varian; Siemens) fitted with a custom head coil. Functional volumes were collected using an oblique coronal slice orientation, roughly perpendicular to the longitudinal hippocampal axis with the constraint that the most anterior slices excluded the eyes. The entire anterior/posterior extent of the brain was covered with the resulting volumes. However, acquisition constraints prevented collection of data for the most superior aspects of the brain, including dorsal aspects of the parietal lobe, as well as the most dorsal aspects of the frontal lobe, which, with the given slice orientation, corresponded only to posterior sections. Thus, most aspects of dorsolateral prefrontal cortex were covered in the functional volumes. All functional scans were acquired using a T_2*-weighted 4-shot spiral sequence: echo time (TE) = 12 ms, repetition time (TR) = 625 ms yielding a total volume acquisition time of 2500 ms, flip angle = 30°. Each functional volume was composed of 19 contiguous 4-mm slices (22 × 22-cm field of view, 64 × 64 matrix, in-plane resolution of 3.44 × 3.44 mm). Each experimental run involved the collection of 160 functional volumes. High-resolution T_1-weighted structural scans were collected in the same scanning session (144 slices, TR = 45 ms, TE = 3 ms, 256 × 256 matrix, in-plane resolution of 0.86 × 0.86 mm with 1-mm slice thickness) for detailed depiction of brain anatomy. Data preprocessing was completed using Brain Voyager QX 1.8 software

(Brain Innovation). Functional images were resampled into 3-mm isotropic voxels, high-pass filtered, coregistered with the anatomical image, and transformed into standardized Talairach space. The resulting images were smoothed using a 3D Gaussian kernel with a full-width at half-maximum value of 6 mm.

4.2.5 Functional Connectivity Analysis

Functional connectivity analyses on PrC were performed using multivariate PLS (McIntosh et al., 1996; McIntosh et al., 2004). To address our question of interest, we applied seed PLS, a multivariate analysis technique that allows for the identification of spatiotemporal patterns of brain activity, with respect to the experimental conditions, by focusing on the covariance of the blood oxygen level–dependent response between the seed region and the rest of the brain across participants. Put another way, seed PLS allows for investigation of task-related changes in functional connectivity of the seed region. This technique works on the entire group data set at once, flattening spatial and temporal information into a 2D data matrix.

In order to investigate the functional connectivity of PrC with other cortical and subcortical regions, we first defined a seed region in PrC. Our selection was guided by the findings from our univariate GLM-based analyses reported in O'Neil et al., (2009), specifically our observation of shared right PrC involvement in perceptual oddball and recognition memory judgments. Due to differences in data interpolation and definition of cortical boundaries (based on voxel intensity) between BrainVoyager and the PLS platform, it was not possible to use the exact coordinates of the PrC region in the right hemisphere that showed this overlap in our previous analyses. Thus, we used a data-driven version of task PLS aiming to obtain a seed region in close vicinity of the region that we previously reported with a similar common involvement in memory and perception. This type of analysis revealed the major sources of task-related differences in activity across the entire functional volume (independent of any seeds), expressed as latent variables (LVs). Task saliences reflect the loading of experimental tasks; associated patterns of brain activity (i.e., singular images) reveal regions that are sensitive to the task distinction captured by the LV. Nonparametric permutation tests can be used to

determine whether the covariance accounted for by the LV differs from chance. In addition, voxel saliences can be tested with nonparametric bootstrap statistics to assess which regions make reliable contributions to the pattern specified in a singular image.

The first LV obtained with this task PLS revealed a distributed activity pattern that differentiated between all experimental conditions on the one hand and the baseline task as well as fixation on the other (explained cross-block covariance = 40.2%, $P < 0.001$ based on 500 permutations). Not surprisingly, brain regions with higher activity in the experimental task as indicated by reliable positive saliences (>3.28 corresponding to $P< 0.001$ as assessed with 100 bootstrap tests) for this LV included large aspects of bilateral occipitotemporal cortex. Critically, a cluster of right-sided PrC voxels was also part of this pattern, replicating results obtained with our prior GLM-based analysis for these data. To specify a seed region in PrC that was well-suited to capture PrC activity across subjects, despite the variable nature of the collateral sulcus (see Pruessner et al., 2002), the 4-voxel cluster that met our salience-based criteria was grown using a 2 nearest-neighbor selection method (centered on Talairach coordinates $x= 25$, $y = 0$, $z = −25$). In this selection process, we ensured, using the anatomical scan averaged across all participants, that no voxels encroached on the hippocampus or amygdala. Due to the documented variability of the anterior collateral sulcus (Pruessner et al., 2002), however, it is impossible to clearly distinguish between the medial and lateral bank of this sulcus on the averaged MR image. Thus, we cannot rule out that aspects of entorhinal cortex were included in the PrC seed in this group-based approach (see Fig. 4.1*B*). Using univariate *t*-tests on activity averaged across all voxels included in this seed region of interest, we confirmed that, like the PrC cluster identified in our original analyses, this region exhibited no significant difference between the difficult recognition memory and perceptual oddball conditions that were matched for accuracy, $t_{17} = 1.63$, $P > 0.05$ and no overall effect of task difficulty,$t_{17} = 1.77$, $P > 0.05$. Consistent with our previous report, we did find an effect of accuracy across the two experimental tasks, $t_{17} = 3.12$, $P < 0.01$. Although the pattern of activity in the task PLS that allowed us to identify the PrC seed also included bilateral regions in the hippocampus (left $x = −16$, $y = −4$, $z = −11$; right $x = 17$, $y = −4$, $z = −8$), these regions did not exhibit any modulation related to accuracy (all $P > 0.05$). Moreover, when used in exploratory seed analyses, we did not see any

differential patterns of connectivity across the perception and memory tasks. Thus, these hippocampal regions were not investigated further (for additional commentary, see Discussion).

Functional data from the described PrC seed region were extracted for the seed PLS analysis. This region was selected from the third lag of the LV, corresponding to the typical peak of the hemodynamic response function. A data matrix was constructed consisting of voxel intensities capturing a temporal window of 15 s following stimulus onset for each trial. This allowed for the consideration of the relationship between activity in the seed region and the rest of the brain throughout the typical duration of the hemodynamic response. Note, however, that no a priori HR function is modeled in this type of analysis. In data-driven approaches, PLS uses singular value decomposition to rotate the data matrix to identify the strongest effects in the data. Here, we used a nonrotated version of seed PLS, in which a priori contrasts restrict the patterns derived (McIntosh et al., 2004; Protzner and McIntosh, 2008). We opted for this nonrotated version as we aimed to test specific hypotheses with 2 contrasts of interest. A singular image is computed for each contrast of interest representing the distributed voxel pattern that embodies it. The strength of the relationship between the singular image and the designated contrast is given by the singular value. In this nonrotated version, the singular image is simply the cross-product of a contrast and the data matrix, and the singular value is the sum of squared voxel values for the singular image. As in the task PLS previously described, statistical assessment was performed using nonparametric permutation tests for the LVs and bootstrap estimation of standard errors for the voxel saliences. The permutation test assesses whether the functional connectivity effect represented in a given LV, captured by the singular value, is sufficiently strong to be considered different from random noise. The standard error estimates of the voxel saliences in each singular image from the bootstrap tests served for assessment of the reliability of the nonzero saliences in significant LVs. Following established criteria for nonparametric tests in PLS analyses (e.g., McIntosh et al., 2004; Protzner and McIntosh, 2008; Stevens et al., 2008), results from the permutation tests were considered significant if they survived $P < 0.05$ (as no correction for multiple comparisons is required), and saliences assessed with bootstrap estimates were considered significant if they met a threshold of 3.28,

corresponding to approximately $P < 0.001$, at a cluster threshold of 5 voxels. All reported coordinates and cluster sizes were obtained for the third lag (TR), corresponding to the typical peak of the hemodynamic response function.

4.2.6 Effective Connectivity Analysis

In an additional analysis, we also employed SEM (LISREL 8.80, Student Edition, Scientific Software Inc.) to examine whether memory and perception tasks involve different patterns of effective connectivity in a simplified, neuroanatomically constrained network that involved a subset of those regions identified with the seed PLS and a connectivity matrix that honored known neuroanatomical connections. Regions included in the model were selected based on theoretical considerations (i.e., prior discussion in the fMRI literature) and robust signs of PrC connectivity as demonstrated by the seed PLS analyses just summarized. All regions were situated in the right hemisphere and included PrC, dorsolateral PFC, ventrolateral PFC, posterior cingulate, superior temporal sulcus, and fusiform gyrus. Corresponding Talairach coordinates for these regions are presented in Tables 4.1 and 4.2. The peak voxel of each region was expanded using a 1 nearest-neighbor method, and activity profiles were extracted for the memory and perception task in each participant based on the average obtained over the third and fourth lag (TR from trial onset). This provided us with 72 data points (18 participants; 4 conditions) for each of these 2 tasks for each region. As our main interest focused on the difference between memory and perception, within subject variance related to accuracy and difficulty manipulations was removed with a residualization procedure previously described (McIntosh and Gonzalez-Lima, 1991). Anatomical connectivity, including directionality, was specified based on reports from the nonhuman primate literature (Suzuki and Amaral, 1994; Morris et al., 1999; Petrides and Pandya, 1999; Petrides and Pandya, 2006; Lavenex et al., 2002; Petrides, 2005; Gerbella et al., 2010). To determine whether effective connectivity differed between the memory and perception tasks, we used a stacked model approach (Mclntosh and Gonzalez-Lima, 1994). Inferential statistics involved comparing a model in which the path coefficients were constrained to be equal across conditions (null model) with a model in which the coefficients were allowed to differ between conditions (alternate model). For each model, a goodness of fit

value, expressed as χ^2, was computed that reflects the extent to which the set of path coefficients reproduced the correlation matrices for all conditions. Inferences were based on the difference in goodness of fit ($\Delta\chi^2$) between the 2 models. Specifically, we examined whether goodness of fit was improved by allowing path coefficients to vary across tasks. Individual paths were examined in 2 different orders to determine whether they contributed to the improved fit of the model. Order of testing was found to have no impact on the results reported.

Table 4.1

Regions exhibiting differential functional connectivity with the PrC seed region during the memory and perceptual task

Region	Hemisphere	Talairach Coordinates			Ratio	Cluster Size
		x	y	z		
Memory > Perception						
*Post Cingulate Cortex	R	5	-28	22	5.07	31
*Inf Frontal Gyrus (VLPFC)	R	44	32	10	4.38	19
Ant Cingulate Cortex	L	-7	47	4	4.37	7
Cerebellum	L	-28	-52	-41	4.37	9
Post Cingulate Cortex	L	-22	-37	16	4.32	13
Thalamus	R	11	-16	19	4.28	14
Perception > Memory						
*Fusiform Gyrus	R	17	-58	-20	-6.64	164
Middle Frontal Gyrus (DLPFC)	R	47	-1	40	-5.20	17
Sup Temporal Gyrus	L	-49	20	1	-5.10	12
*Sup Temporal Sulcus	R	38	-16	-11	-4.88	23
Sup Frontal Sulcus	L	-28	44	43	-4.88	12
Middle Frontal Gyrus (DLPFC)	L	-25	32	34	-4.76	32
Fusiform Gyrus	L	-25	-70	-26	-4.50	21
Fusiform Gyrus	L	-43	-34	-20	-4.35	7
Cerebellum	B	2	-43	-11	-4.16	8

Note. Talairach Coordinates indicate peak voxel. Bootstrap ratios all reflect a significance of $p<.001$, min cluster size of 5 voxels, lag 3. VLPFC - ventrolateral PFC; DLPFC – dorsolateral PFC.

*Regions selected for SEM

Table 4.2

Regions exhibiting common increased functional connectivity with the PrC seed region during the experimental tasks as compared to the baseline task.

Region	Hemisphere	Talairach Coordinates			Ratio	Cluster Size
		x	y	z		
*Middle Frontal Gyrus (DLPFC)	R	29	35	25	7.48	80
Sup Frontal Gyrus (DLPFC)	L	-22	65	10	6.22	9
Cerebellum	R	38	-64	-29	5.60	18
Pons	L	-1	-25	-17	5.54	19
Middle Frontal Gyrus (DLPFC)	R	41	20	28	5.29	83
Medial Sup Frontal Gyrus	R	8	50	34	5.27	6
Thalamus	L	-4	-22	1	4.65	12
Cerebellum	L	-37	-55	-29	4.55	8
Sup Frontal Gyrus	R	23	53	10	4.54	11
Middle Frontal Gyrus (DLPFC)	L	-43	20	37	4.51	19
Cerebellum	L	-16	-67	-35	4.44	11
Caudate	R	8	20	16	4.44	7
Sup Temporal Gyrus	L	-40	17	-23	4.43	17
Retrosplenial Cortex	L	-7	-40	7	4.40	7
Lingual Gyrus	L	-4	-73	-20	4.34	44
Retrosplenial Cortex	R	14	-40	13	4.32	17
Medial Sup Frontal Gyrus (DLPFC)	L	-13	50	34	4.32	6
Fusiform Gyrus	L	-28	-79	-23	4.28	8
Fusiform Gyrus	L	-28	-40	-20	4.27	22
Middle Temporal Gyrus	L	-34	-55	10	4.13	11
Temporal Pole	L	-4	65	4	4.12	6
Cerebellum	L	-22	-28	-32	3.93	6
Middle Frontal Gyrus (DLPFC)	R	38	47	7	3.72	5

Note. Talairach Coordinates indicate peak voxel Bootstrap ratios all reflect a significance of $p<.001$, minimum cluster size of 5 voxels, lag 3. DLPFC – dorsolateral PFC.

* Region selected for SEM.

4.3 Results

To address our main question of interest, we first determined whether we could identify a significant LV that would reflect distinct patterns of functional connectivity between the PrC seed region and the rest of the brain for the perceptual oddball and recognition memory tasks. The LV that was associated with this a priori contrast was found to be significant and accounted for 11.0% of cross-block covariance ($P < 0.05$, see Fig. 4.2). Reliable positive saliences on the corresponding singular image, which reflect an increased positive coupling between PrC and the rest of the brain during the memory as compared to the perceptual task, are listed in Table 4.1. Consistent with our predictions, the regions that showed the most reliable increase in coupling were right ventrolateral PFC and a posterior midline region in posterior cingulate cortex at the border to retrosplenial cortex. Figure 4.3 shows the time course of the correlations between PrC and these selected regions. Regions with reliable negative saliences that displayed an increased positive coupling during the perception task were found in bilateral posterior fusiform gyrus and ventral occipital regions as well as in bilateral superior temporal sulcus (see Figs 4.2 and 4.3). Visual inspection of the correlation between the brain scores (i.e., the dot product of the voxel salience and fMRI data) and the fMRI signal in the seed region for each experimental condition showed that the task-dependent changes in the correlation between the PrC seed and the regions identified in the singular image of LV 1 were comparable across the easy and difficult task conditions (see Fig. 4.2). This observation was confirmed statistically by the fact that a targeted task-difficulty contrast did not account for a significant portion of cross-block covariance ($P > 0.05$).

Given that our PrC seed was selected based on its common involvement in the memory and perception tasks, we also investigated whether activity in PrC showed a pattern of coupling with other brain regions that was common to both tasks. Toward this end, we examined the contrast between the luminance baseline task and all perceptual and memory conditions. The corresponding LV was significant and accounted for 39.7% of cross-block covariance ($P < 0.001$). The pattern of regions that showed an increased positive coupling with PrC in both tasks, as compared with the luminance baseline, is displayed in Figure 4.4 (see also Table 4.2). This pattern included several foci in bilateral

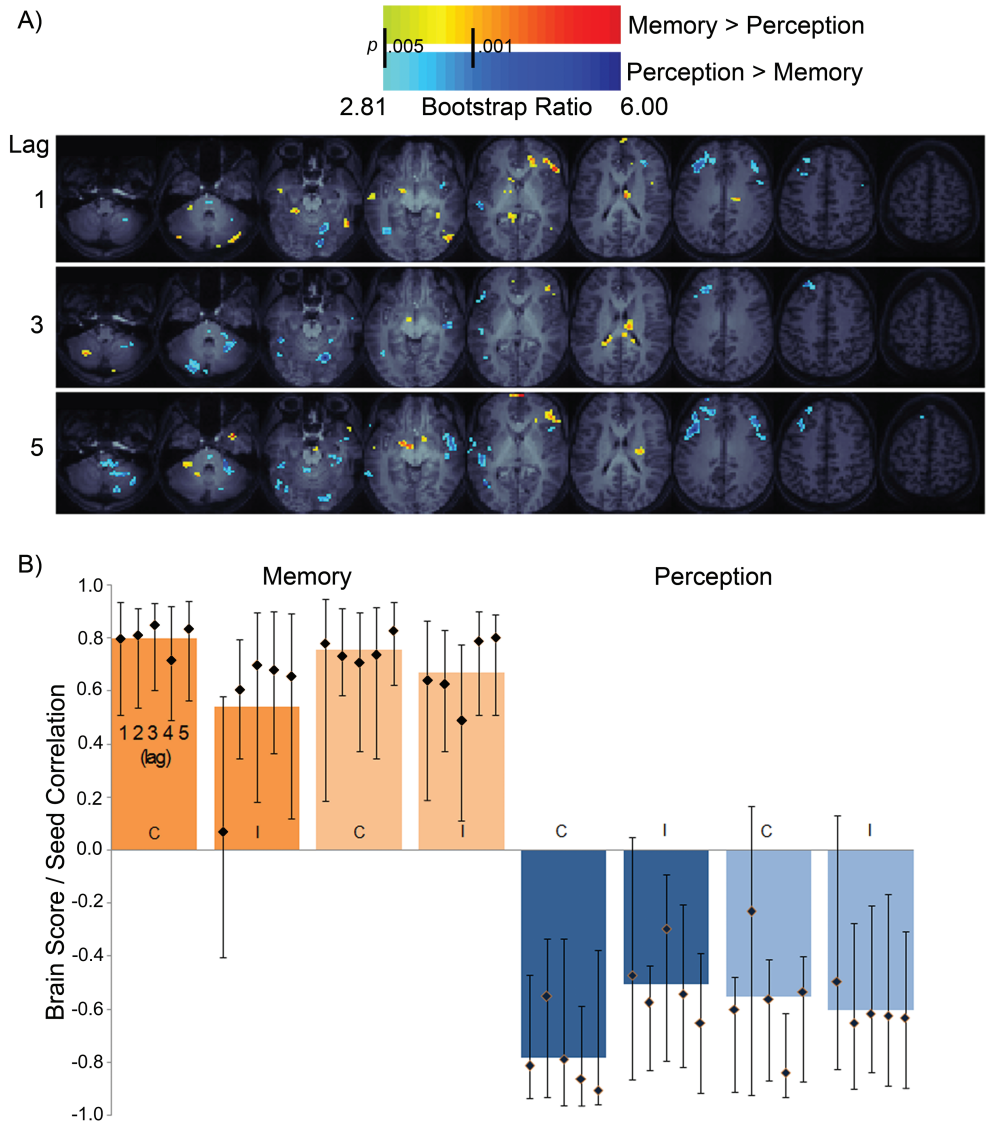

Figure 4.2. (A) Pattern of distinct functional connectivity revealed with the contrast between recognition memory and perceptual discrimination for the PrC seed region. Maps are thresholded at $P = 0.005$ for visualization purposes. (B) Associated LV demonstrating how this pattern of activity mapped onto experimental conditions. Bar plot depicts correlation between brain scores and PrC seed activity. Dark colors = difficult trial conditions, light colors = easy trial conditions, C = correct trials, I = incorrect trials. Lags 1-5 correspond to 2.5-s intervals encompassing the duration of the hemodynamic response within a trial. Error bars represent 95% confidence intervals derived by bootstrap estimation.

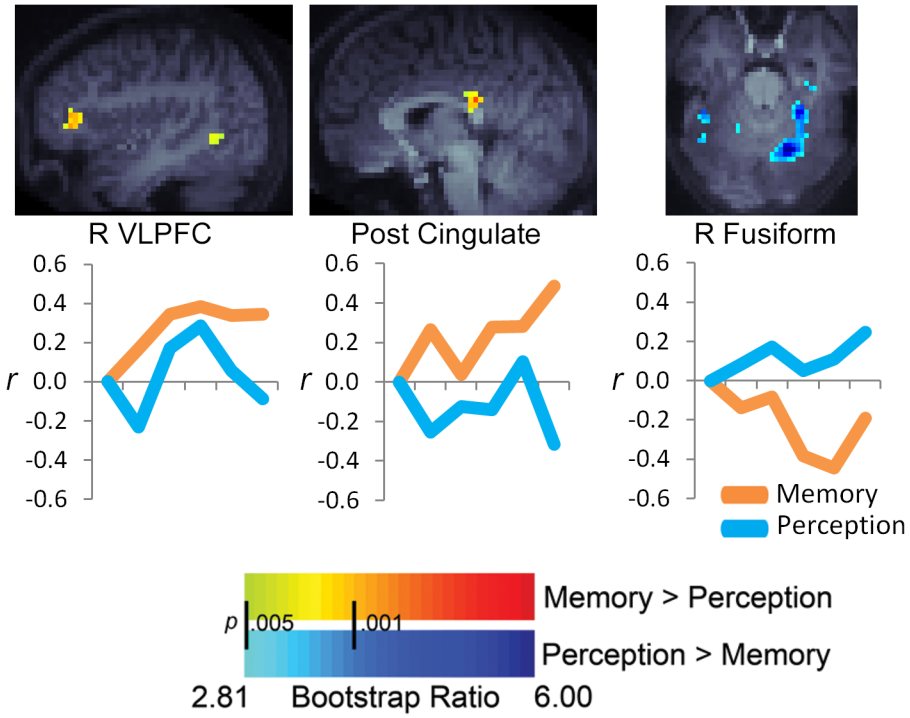

Figure 4.3. Functional coupling between PrC and selected regions that were part of the pattern showing differential connectivity for memory and perception illustrated in Figure 2. Time courses show correlations of activity between the seed and a 9-mm cube centered on the peak voxel of each region over the course of a trial (hatch marks on x-axis indicate 2.5-s lag intervals following stimulus onset). Note that such coupling is not constrained to follow the typical hemodynamic response function.

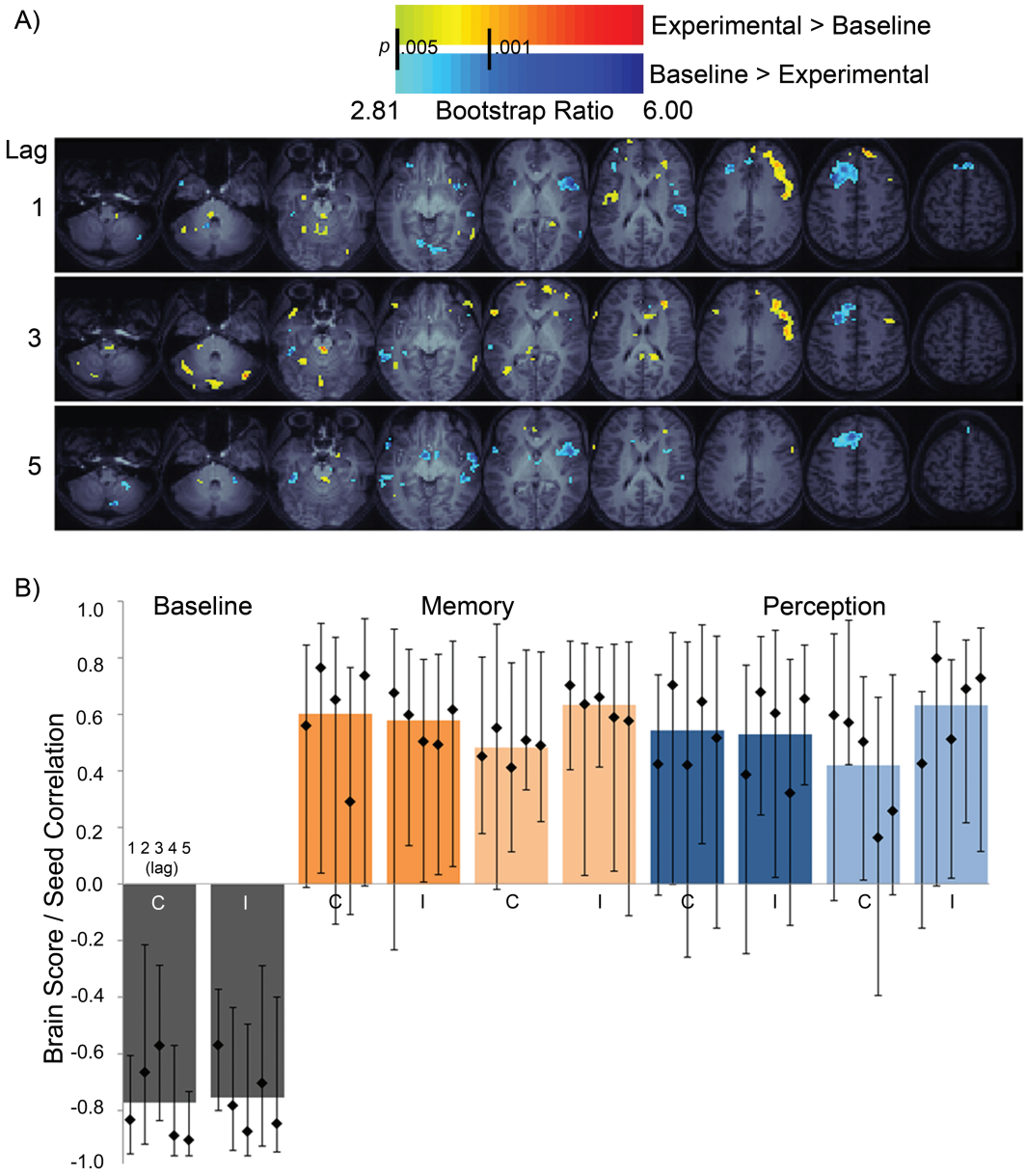

Figure 4.4. (A) Pattern of common functional connectivity revealed with the contrast between the two experimental tasks and the luminance baseline task for the PrC seed region. (B) Associated LV demonstrating how this pattern of activity mapped onto experimental conditions. Bar plot depicts correlation between brain scores and PrC seed activity. For additional information, see Figure 4.2 caption.

dorsolateral PFC, with the largest cluster and the highest bootstrap ratio present in the right hemisphere (as shown in Table 4.2).

In a final step of our functional connectivity analyses, we aimed to determine whether the differential coupling we observed between PrC and other cortical regions for the memory versus perception task was related to interindividual differences in behavioral accuracy. To examine this possibility, we assessed the correlations between the strength of the relationship between the seed region and the brain scores with behavioral performance for the memory and oddball tasks. Put another way, we determined whether behavioral performance was related to how strongly the pattern between the seed and the singular image was expressed in each participant. Brain scores offer an index of how strongly individual participants express the pattern captured by a given LV in a given task. Collapsing across easy and difficult conditions, we observed that participants with higher behavioral accuracy in the memory task also showed stronger functional connectivity between the PrC seed and the pattern of brain regions identified with our first LV, showing a tighter positive coupling in the memory task, $r_{16} = 0.451$, $P < 0.05$. No such relationship was found for behavioral performance on the perceptual task $r_{16} = -0.209$, $P > 0.05$.

In a follow-up analysis, we employed SEM to examine changes in effective connectivity for a subset of regions that were identified with seed PLS and that are of particular interest in the context of the functional neuroimaging literature reviewed in the Introduction (see Fig. 4.5). Generally speaking, we aimed to explore connectivity in a model that probed interactions between PrC, prefrontal regions implicated in executive control, and regions implicated in face processing. The model included regions with differences in functional connectivity with PrC across tasks (ventrolateral PFC, posterior cingulate, superior temporal sulcus, and fusiform gyrus), as well as a region in dorsolateral PFC with a common pattern of connectivity. In the first step of model assessment, an omnibus test revealed that the alternative model provided improved fit over the null model, suggesting memory and perception tasks were associated with differential patterns of effective connectivity, $\Delta\chi^2(13) = 34.97$, $P < 0.001$. In a second step, we explicitly tested whether task-related differences in the pattern of effective

connectivity would also emerge when only direct connections with PrC were considered, that is, were allowed to vary across tasks, with all other connections forced to maintain fixed values. In comparison with the null model, we again found a significant increase in model fit, $\Delta\chi^2(5) = 15.67$, $P < 0.01$. Finally, testing of individual path coefficients (Fig. 4.5) revealed that connections with the most noticeable (i.e., individually significant) changes across tasks involving PrC were those between PrC and ventrolateral PFC as well as between PrC and posterior cingulate cortex (Fig. 4.5 and Table 4.3). Other connections with significant task-related differences were found between ventrolateral PFC and dorsolateral PFC and between ventrolateral PFC and superior temporal sulcus (see Table 4.3).

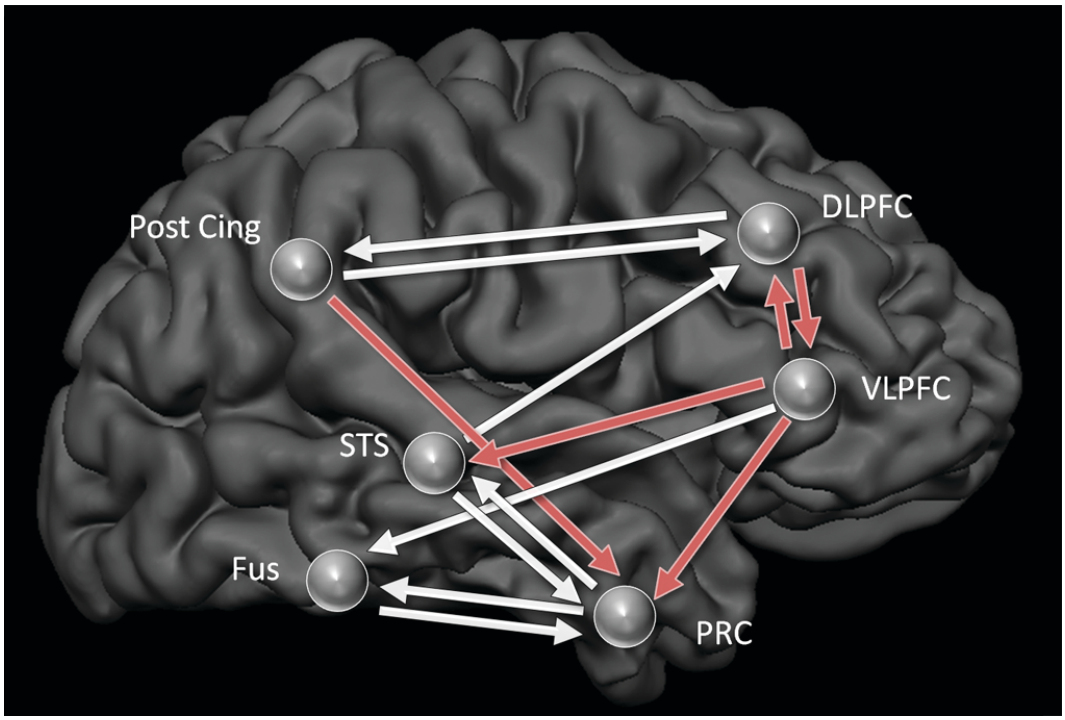

Figure 4.5. Anatomical model and effective connectivity changes across tasks in the SEM analyses. Connections exhibiting significant task-related changes in effective connectivity are shown in red. Corresponding path coefficients are listed in Table 4.3. Generally, the pattern of change was such that coupling was more positive in memory than in perception. For ventrolateral PFC and PrC, the change was in the same direction but the path coefficients took on negative values in both cases.

Table 4.3

Path coefficients derived from SEM analyses for connections that showed significant differences between memory and perception conditions

Region			Memory	Perception
Ventrolateral PFC	→	Perirhinal Cortex	-0.19	-0.38
Ventrolateral PFC	→	Dorsolateral PFC	0.13	-0.06
Ventrolateral PFC	→	Sup Temp Sulcus	0.09	-0.17
Dorsolateral PFC	→	Ventrolateral PFC	0.12	-0.08
Post Cing Cortex	→	Perirhinal Cortex	0.28	-0.04

Note. All other path coefficients did not significantly differ.

4.4 Discussion

Using a multivariate seed-correlation approach, we examined task-related modulations of functional connectivity between PrC and the rest of the brain that pertain to recognition memory and perceptual discrimination of faces. Although right PrC showed a comparable involvement in our forced-choice memory and perceptual oddball tasks, as previously reported (O'Neil et al., 2009), it exhibited distinct patterns of functional connectivity during execution of these tasks. SEM-based examination of PrC connectivity within a network of selected regions identified with our seed analysis also revealed that distinct patterns of effective connectivity can be detected for regions known to be directly connected with PrC.

Right ventrolateral PFC and posterior cingulate cortex were part of the network of brain regions that exhibited stronger functional connectivity with PrC in recognition memory than in perceptual discrimination. Conversely, ventral occipital regions, aspects of bilateral posterior fusiform gyrus, as well as bilateral superior temporal sulcus were part of the network of regions that displayed stronger coupling with PrC in perceptual discrimination than in recognition memory. Furthermore, the strength of the coupling in the memory condition for the pattern of regions that discriminated between memory and perception was related to interindividual differences in behavioral accuracy on that task. Contrasting with these differences between recognition memory and perceptual discrimination, we also identified a pattern of PrC functional connectivity common to these experimental tasks, when compared with the luminance baseline task; this pattern included several foci in right dorsolateral PFC. To our knowledge, these findings are the first to reveal that PrC dynamically supports performance in mnemonic and perceptual tasks through shared and distinct patterns of functional interactions with other cortical regions.

The current investigation was guided by a representational theory of PrC functioning that contrasts with the classic view, which holds that the MTL operates as an integrated system that is dedicated to declarative memory. The representational view posits MTL contributions to a task are related to computational demands involved in

creating specific types of representations, and that a common, highly integrated representation in PrC supports both memory and perception when discrimination of stimuli cannot be based on simple perceptual features (Murray and Bussey, 1999;Murray et al., 2007). Within such a framework, the question emerges as to how the neural correlates of perceptual discrimination and recognition memory differ when representational demands are closely matched. The present findings suggest that such differences are reflected in distinct patterns of functional interactions between PrC and other cortical regions. In functional terms, such differences in connectivity likely pertain to processes of cross-cortical integration given they are also related to the resulting quality of the discrimination process, that is, its accuracy.

Patterns of PrC functional connectivity in the current study were found to be related to demands that were both distinct and common for the 2 experimental tasks. In both cases, these patterns included regions of PFC. While the current experiment was not designed to pinpoint the specific control processes that are distinct and those that are shared, the fMRI literature reviewed in the Introduction allowed us to make some predictions concerning task-related involvement of PFC. One of the regions we anticipated to exhibit differential coupling with PrC during performance of the recognition memory versus the perceptual oddball task was right ventrolateral PFC; this region has previously been linked to the evaluation of perceptual information when the latter is required for stimulus-based or contextually based recognition (Kostopoulos and Petrides, 2003; Dobbins and Wagner, 2005) and to mnemonic intentions when complex perceptual stimuli are being viewed (Dove et al., 2006). Theories that emphasize the role of PFC in behavioral control processes suggest that such control may come about through top-down biasing of posterior cortical regions involved in perceptual analyses (e.g., Desimone and Duncan, 1995). In forced-choice recognition memory tasks, like the one used in the present study, such top-down control may be critical for increasing subtle differences in perceived memory signal associated with the perceptually highly similar choices in the display (as an index of familiarity). Right ventrolateral PFC, specifically, has been proposed to amplify the gain on signals activated by retrieval probes in recognition memory tasks (Dobbins and Wagner, 2005). As memory signals are irrelevant for the oddball task, the corresponding negative path coefficients for the

connections between ventrolateral PFC and PrC, as well as between ventrolateral PFC and the superior temporal sulcus, revealed though our SEM analyses can be interpreted as reflecting a process of inhibition. Such a process would be of particular importance in the context of a task design that mixes memory and perceptual trials, as in the current study. That the introduction of explicit memory demands led to a switch from a negative to a positive coupling in effective connectivity between ventrolateral PFC and the superior temporal sulcus, a region frequently implicated in the perceptual representation of faces in past fMRI research (Ishai, 2008; Liu et al., 2010), is also in line with this notion. For PrC, however, the SEM findings for the memory condition appear less clear-cut. That the coefficient for the connection between ventrolateral PFC and PrC shifted toward smaller negative values could suggest that PFC mediated gain of memory signals may also come about through partial release from inhibition.

Another brain region that showed differential coupling in functional and effective connectivity for recognition memory as compared with perceptual oddball discrimination was found in posterior cingulate cortex. Activation in this region has previously been reported in other studies involving recognition memory for faces. For example, increases in posterior cingulate activity have been found to track increases in familiarity induced through multiple exposures of faces over the course of an experimental session (Kosaka et al., 2003). Evidence for a critical role of this region in the discrimination between familiar and unfamiliar faces has also come from research on individuals with congenital prosopagnosia, that is, individuals who exhibit consistent and lasting impairments in face recognition. Specifically, although such individuals were reported to show normal effects of repetition in the fusiform gyrus, posterior cingulate regions did not discriminate between previously familiar and novel faces as demonstrated in healthy control participants (Avidan and Behrmann, 2009). While neither these findings nor those from the present study offer insight as to the specific functional contributions of the posterior cingulate to the recognition of familiar faces, one possibility raised in the context of other research is that it could be involved in orienting attention to internally generated representations (Cabeza et al., 2003). Regardless of whether this particular interpretation holds to be true, the observed task-related changes in patterns of functional and effective connectivity between posterior cingulate cortex and PrC indicate that integration of

cortical signals involved in recognition judgments extends beyond the interplay between the MTL and PFC.

At first glance, it may seem surprising that the pattern of PrC connectivity that differentiated recognition memory from perceptual discrimination did not include the hippocampus. However, although it is well established that the hippocampus plays a critical role in recognition memory, recent research suggests that its contributions are specific to processes of recollection, that is, the recovery of contextual associations pertaining to a prior encounter with the stimulus that is being judged, rather than to recognition more broadly (Brown and Aggleton, 2001; Eichenbaum et al., 2007). Forced-choice recognition memory tasks that require discrimination between perceptually highly similar stimuli, such as the one used in the current experiment, encourage recognition decisions based on a comparison of subtle differences in the relative familiarity of all concurrently presented items in the display (Migo et al., 2009). This retrieval process has been linked to PrC functioning and has been proposed to rely on specific computational mechanisms that are different from those that support hippocampally mediated recognition (Norman and O'Reilly 2003; Norman 2010). In line with this notion, human lesion research has shown that some individuals with selective hippocampal damage are not impaired in making recognition judgments in forced-choice memory tasks with high perceptual similarity between targets and lures, while clearly showing deficits in recollection (Holdstock et al., 2002; cf., Jeneson et al., 2010). From this perspective, the lack of hippocampal involvement in the current set of results is in fact expected.

Our functional connectivity analyses also revealed brain regions that exhibited stronger coupling with PrC in the perceptual discrimination as compared with the recognition memory task. Such increased functional connectivity was observed in posterior cortical regions previously characterized as being part of a face processing network (Gobbini and Haxby, 2007; Barbeau et al., 2008; Ishai, 2008), including the superior temporal sulcus and the fusiform gyrus, as well as in bilateral dorsolateral PFC. The higher overall similarity of the faces in the oddball as compared with memory displays, which was introduced to equate task difficulty, may have contributed to an increased requirement for integration of activity in ventral visual pathway structures with

PrC. Furthermore, to identify the oddball in our perceptual discrimination task, the perceptual similarity between all stimuli must be compared explicitly. This places heavy demands on maintenance of multiple faces in working memory; by contrast, a direct assessment of perceptual similarity in the display is not required in forced-choice recognition tasks (for discussion, see Dobbins and Han, 2006). Prior research on the effects of working memory load for faces on activity in the posterior fusiform gyrus suggests that the increased functional connectivity between this region and PrC in the current study may be related to working memory demands (Druzgal and D'Esposito, 2001; Druzgal and D'Esposito, 2003). However, given that our effective connectivity analyses did not reveal any significant differences in path coefficients for these particular connections across tasks, it remains a possibility that the differences in functional connectivity we observed are indirect and reflect influences mediated by other structures. Further research is needed to elucidate how PrC, fusiform gyrus, and the superior temporal sulcus jointly support the representation of faces under varying perceptual and working memory demands, and how their activity is influenced by other regions.

Turning to the pattern of PrC connectivity common to both experimental tasks, we found that it included right dorsolateral PFC as predicted. Again, the design of our study does not allow us to specify the exact role that this region plays across domains. Common coupling with PrC in both memory and perceptual oddball tasks may reflect a role of dorsolateral PFC in attentional processes that are shared across domains (e.g., Cabeza et al.2003). In the current experimental paradigm, all trials required processing of multiple simultaneously presented faces and the selection of a single target. Prior research using a visual target detection task, involving the presentation of complex visual stimuli from different categories, indicates that right dorsolateral PFC responds comparably to the presentation of both target and same-category foil stimuli but less so to stimuli categories irrelevant for the search at hand (Hampshire et al., 2007). This finding suggests a broad attentional tuning of dorsolateral PFC to the stimulus category relevant for the task goal, rather than to a specific target item. Connectivity of dorsolateral PFC with PrC during the experimental tasks could thus reflect the interplay between regions supporting attention to items within a stimulus class and those supporting individual item representations, respectively. Such interplay was reduced in the luminance baseline task

as PrC-based representations would be ill-suited for supporting discrimination of simple features, such as brightness. While this attentional account of shared connectivity across our memory and perception task is appealing, we acknowledge that it remains speculative at present, and that other interpretations are viable as well. An alternate view, for example, that has been suggested, assigns dorsolateral PFC a role in integrating information distributed over many cortical regions into complex but unified representations (e.g., Naghavi and Nyberg, 2005). Theoretical consideration aside, as neuroanatomical findings suggest only sparse if any direct connections between dorsolateral PFC and PrC in primates (Petrides and Pandya, 1999; Petrides and Pandya, 2006), a full account of interactions between these regions must ultimately also take into consideration the role of other mediating structures.

In closing, we would like to emphasize that our general finding of task-dependent modulations of functional connectivity does not imply that the regions we identified to be differentially connected with PrC in our recognition memory and perceptual oddball tasks are uniquely specialized for declarative memory and perceptual processing, respectively. It also does not entail that these regions are always recruited together with PrC in a fixed manner when recognition memory or perceptual discrimination tasks are being performed. Rather, the patterns of functionally connected regions may be better understood as flexibly deployed network configurations that are optimized for specific processing goals dictated by many different task demands and parameters (e.g., McIntosh, 1999; Fuster, 2009). Further research is necessary to determine how these patterns change, for example, when the format of the recognition task is changed from forced choice to yes/no or when the perceptual task requires matching of stimuli rather than detection of an oddball. Regardless of the outcome of such future research, the current findings offer critical first evidence that, even when MTL structures show a similar involvement in recognition memory and perceptual discrimination, differential neural mechanisms are present at the level of interplay between the MTL and other cortical regions.

4.5 References

Avidan, G., & Behrmann, M. (2009). Functional MRI reveals compromised neural integrity of the face processing network in congenital prosopagnosia. *Current Biology*, *19*, 1146-1150. doi: 10.1016/j.cub.2009.04.060

Axmacher, N., Schmitz, D. P., Wagner, T., Elger, C. E., & Fell J. (2008). Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study. *Journal of Neuroscience*, *28*, 7304-7312. doi: 10.1523/JNEUROSCI.1778-08.2008

Barbeau, E. J., Taylor, M. J., Regis, J., Marquis, P., Chauvel, P., & Liégeois-Chauvel, C. (2008). Spatio temporal dynamics of face recognition. *Cerebral Cortex*, *18*, 997-1009. doi: 10.1093/cercor/bhm140

Barense, M. D., Henson, R. N. A., Lee A. C. H., & Graham K. S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*, 389-401. doi: 10.1002/hipo.20641

Baxter, M. G. (2009). Involvement of Medial Temporal Lobe Structures in Memory and Perception. *Neuron*, *61*, 667-677. doi: 10.1016/j.neuron.2009.02.007

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*, *2*, 51-61. doi: 10.1038/35049064

Buckley, M. J., Booth, M. C., Rolls, E. T., & Gaffan, D. (2001). Selective perceptual impairments after perirhinal cortex ablation. *Journal of Neuroscience*, *21*, 9824-9836.

Buckley, M. J., & Gaffan, D. (1997). Impairment of visual object-discrimination learning after perirhinal cortex ablation. *Behavorial Neuroscience*, *111*, 467-475.

Buckley, M. J., & Gaffan, D. (2006). Perirhinal cortical contributions to object perception. *Trends in Cognitive Science*, *10*, 100-7. doi: 10.1016/j.tics.2006.01.008

Buckner, R. L., & Wheeler, M. E. (2001). The cognitive neuroscience of remembering. *Nature Reviews Neuroscience*, *2*, 624-634.

Bussey, T. J., Saksida, L. M., & Murray, E.A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *European Journal of Neuroscience*, *15*, 365-374. doi: 10.1046/j.0953-816x.2001.01851.x

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2003). Impairments in visual discrimination after perirhinal cortex lesions: testing 'declarative' vs. 'perceptual-

mnemonic' views of perirhinal cortex function. *European Journal of Neuroscience*, *17*, 649-660. doi: 10.1046/j.1460-9568.2003.02475.x

Cabeza, R., Dolcos, F., Prince, S. E., Rice, H. J., Weissman, D. H, & Nyberg, L. (2003). Attention-related activity during episodic memory retrieval: a cross-function fMRI study. *Neuropsychologia*, *41*, 390-399. doi: http://dx.doi.org/10.1016/S0028-3932(02)00170-7

Cansino, S., Maquet, P., Dolan, R. J., & Rugg, M. D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cerebral Cortex*, *12*, 1048-1056. doi: 10.1093/cercor/12.10.1048

Cate, A. D., & Köhler, S. (2006). The missing whole in perceptual models of perirhinal cortex. *Trends in Cognitive Science*, *10*, 396-397. doi: 10.1016/j.tics.2006.07.004

Cowell, R., Bussey, T., & Saksida, L. (2009). Functional Dissociations within the Ventral Object Processing Pathway: Cognitive Modules or a Hierarchical Continuum? *Journal of Cognitive Neuroscience*, *22*, 2460-2479. doi: 10.1162/jocn.2009.21373

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *Journal of Neuroscience*, *26*, 12186-12197. doi: 10.1523/JNEUROSCI.2818-06.2006

Dale, A. M. (1999). Optimal experimental design for event-related fMRI. *Human Brain Mapping*, *8*, 109-114.

Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. Journal of *Neurophysiology*, 96, 1902-1911. doi: 10.1152/jn.01029.2005

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, *18*, 193-222. doi: 10.1146/annurev.ne.18.030195.001205

Devlin, J. T., & Price, C. J. (2007). Perirhinal contributions to human visual perception. *Current Biology*, *17*, 1484-1488. doi: 10.1016/j.cub.2007.07.066

Dobbins, I. G., Foley, H., Schacter, D. L., & Wagner, A. D. (2002). Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron*, *35*, 989-996. doi: http://dx.doi.org/10.1016/S0896-6273(02)00858-9

Dobbins, I. G., & Han, S. (2006). Isolating rule- versus evidence-based prefrontal activity during episodic and lexical discrimination: a functional magnetic resonance imaging investigation of detection theory distinctions. *Cerebral Cortex*, *16*, 1614-1622. doi: 10.1093/cercor/bhj098

Dobbins, I. G., & Wagner, A. D. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cerebral Cortex*, *15*, 1768-1778. doi: 10.1093/cercor/bhi054

Dove, A., Brett, M., Cusack, R., & Owen, A. M. (2006). Dissociable contributions of the mid-ventrolateral frontal cortex and the medial temporal lobe system to human memory. *Neuroimage*, *31*, 1790-1801. doi: 10.1016/j.neuroimage.2006.02.035

Druzgal, T. J., & D'Esposito, M. (2003). Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *Journal of Cognitive Neuroscience, 15*, 771-784. doi: 10.1162/089892903322370708

Druzgal, T. J., & D'Esposito, M. (2001). Activity in fusiform face area modulated as a function of working memory load. *Cognitive Brain Research*, *10*, 355-364. doi: http://dx.doi.org/10.1016/S0926-6410(00)00056-2

Dudukovic, N. M., & Wagner, A. D. (2007). Goal-dependent modulation of declarative memory: neural correlates of temporal recency decisions and novelty detection. *Neuropsychologia*, *45*, 2608-2620. doi: 10.1016/j.neuropsychologia.2007.02.025

Eacott, M. J., Gaffan, D., & Murray, E. A. (1994). Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. *European Journal of Neuroscience*, *6*, 1466-1478.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The Medial Temporal Lobe and Recognition Memory. *Annual Review of Neuroscience*, *30*, 123-152. doi: 10.1146/annurev.neuro.30.051606.094328

Friston, K. (2002). Beyond phrenology: what can neuroimaging tell us about distributed circitry? *Annual Review of Neuroscience*, *25*, 221-250. doi: 10.1146/annurev.neuro.25.112701.142846

Fuster, J. M. (2009). Cortex and memory: emergence of a new paradigm. *Journal of Cognitive Neuroscience*, *21*, 2047-2072. doi: 10.1162/jocn.2009.21280

Gerbella, M., Belmalih, A., Borra, E., Rozzi, S., & Luppino, G. (2010). Cortical connections of the macaque caudal ventrolateral prefrontal areas 45A and 45B. *Cerebral Cortex*, *20*, 141-168. doi: 10.1093/cercor/bhp087

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia*, *45*, 32-41. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2006.04.015

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*, 831-853. doi: 10.1016/j.neuropsychologia.2010.01.001

Habib, R., McIntosh, A. R., Wheeler, M. A., & Tulving E. (2003). Memory encoding and hippocampally-based novelty/familiarity discrimination networks. *Neuropsychologia*, *41*, 271-279. doi: http://dx.doi.org/10.1016/S0028-3932(02)00160-4

Hampshire, A., Duncan, J., & Owen A. M. (2007). Selective tuning of the blood oxygenation level-dependent response during simple target detection dissociates human frontoparietal subregions. *The Journal of Neuroscience*, *27*, 6219-6223. doi: 10.1523/JNEUROSCI.0851-07.2007

Han, S., Huettel, S. A., & Dobbins, I. G. (2009). Rule-dependent prefrontal cortex activity across episodic and perceptual decisions: an fMRI investigation of the criterial classification account. *Journal of Cognitive Neuroscience*, *21*, 922-937. doi: 10.1162/jocn.2009.21060

Hayama, H. R., & Rugg, M. D. (2009). Right dorsolateral prefrontal cortex is engaged during post-retrieval processing of both episodic and semantic information. *Neuropsychologia*, *47*, 2409-2416. doi: 10.1016/j.neuropsychologia.2009.04.010

Heekeren, H. R., Marrett, S., & Ungerleider, L. G. (2008). The neural systems that mediate human perceptual decision making. *Nature Reviews Neuroscience*, *9*, 467-479. doi: 10.1038/nrn2374

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., & Dolan R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience*, *19*, 3962-3972.

Holdstock, J. S, Mayes, A. R., Roberts, N., Cezayirli, E., Isaac, C. L., O'Reilly, R. C., & Norman, K. A. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus*, *12*, 341-351. doi: 10.1002/hipo.10011

Ishai, A. (2008). Let's face it: it's a cortical network. *Neuroimage*, *40*, 415-419. doi: 10.1016/j.neuroimage.2007.10.040

Jeneson, A., Mauldin, K. N., & Squire. L. R. (2010). Intact working memory for relational information after medial temporal lobe damage. *Journal of Neuroscience*, *30*, 13624-13629. doi: 10.1523/JNEUROSCI.2895-10.2010

Köhler, S., McIntosh, A. R., Moscovitch, M., & Winocur, G. (1998). Functional interactions between the medial temporal lobes and posterior neocortex related to episodic memory retrieval. *Cerebral Cortex*, *8*, 451-461.

Kosaka, H., Omori, M., Iidaka, T., Murata, T., Shimoyama, T., Okada, T., Sadato, N., Yonekura, Y., & Wada, Y. (2003). Neural substrates participating in acquisition of facial familiarity: an fMRI study. *Neuroimage*, *20*, 1734-1742. doi: 10.1016/S1053-8119(03)00447-6

Kostopoulos, P., & Petrides, M. (2003). The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval. *European Journal of Neuroscience*, *17*, 1489-1497. doi: 10.1046/j.1460-9568.2003.02574.x

Lavenex, P., Suzuki, W. A., & Amaral, D. G. (2002). Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *Journal of Computational Neurology*, *447*, 394-420. doi: 10.1002/cne.10243

Lee, A. C., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., Hodges, J. R., & Graham, K. S. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*, *43*, 1-11. doi: 10.1016/j.neuropsychologia.2004.07.017

Lee, A. C., Buckley, M. J., Gaffan, D., Emery, T., Hodges, J. R., & Graham, K. S. (2006). Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: a double dissociation in dementia. *Journal of Neuroscience*, *26*, 5198-5203. doi: 10.1523/JNEUROSCI.3157-05.2006

Lee, A. C., Scahill, V. L., & Graham, K. S. (2007). Activating the Medial Temporal Lobe during Oddity Judgment for Faces and Scenes. *Cerebral Cortex*, *18*, 683-696. doi: 10.1093/cercor/bhm104

Liu, J., Harris, A., & Kanwisher, N. (2010). Perception of face parts and face configuration: An fMRI study. *Journal of Cognitive Neurosciemce*, *22*, 203-211. doi: 10.1162/jocn.2009.21203

Marklund, P., Fransson, P., Cabeza, R., Petersson, K. M., Ingvar, M., & Nyberg, L. (2007). Sustained and transient neural modulations in prefrontal cortex related to declarative long-term memory, working memory, and attention. *Cortex*, *43*, 22-37. doi: 10.1016/S0010-9452(08)70443-X

Mayer, J. S., Bittner, R. A., Nikolić, D., Bledowski, C., Goebel, R., & Linden, D. E. J. (2007). Common neural substrates for visual working memory and attention. *Neuroimage*, *36*, 441-453. doi: 10.1016/j.neuroimage.2007.03.007

McCormick, C., Moscovitch, M., Protzner, A. B., Huber, C. G., & McAndrews, M. P. (2010). Hippocampal-neocortical networks differ during encoding and retrieval of relational memory: Functional and effective connectivity analyses. *Neuropsychologia*, *48*, 3272-3281. doi: 10.1016/j.neuropsychologia.2010.07.010

McIntosh, A. R., & Gonzalez-Lima, F. (1991). Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system. *Brain Research*, *547*, 295-302.

Mclntosh, A., & Gonzalez-Lima, F. (1994). Structural equation modeling and its application to network analysis in functional brain imaging. *Human Brain Mapping*, *2*, 2-22. doi: 10.1002/hbm.460020104

McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage*, *3*, 143-157.

McIntosh, A. R. (1999). Mapping cognition to the brain through neural interactions. *Memory*, 7, 523-548. doi: 10.1080/096582199387733

McIntosh, A. R., Rajah, M. N., & Lobaugh, N. J. (2003). Functional connectivity of the medial temporal lobe relates to learning and awareness. *Journal of Neuroscience*, *23*, 6520-6528.

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *Neuroimage*, *23*, 764-775. doi: 10.1016/j.neuroimage.2004.05.018

Migo, E., Montaldi, D., Norman, K. A., Quamme, J. R., & Mayes, A. (2009). The contribution of familiarity to recognition memory is a function of test format when using similar foils. *Q J Exp Psychol Colchester*, *62*, 1198-1215. doi: 10.1080/17470210802391599

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review in Neuroscience*, *24*, 167-202. doi: 10.1146/annurev.neuro.24.1.167

Mitchell, K. J., & Johnson, M. K. (2009). Source Monitoring 15 Years Later: What Have We Learned From fMRI About the Neural Mechanisms of Source Memory? *Psychology Bulletin*, *135*, 638-677. doi: 10.1037/a0015849

Morris, R., Petrides, M., & Pandya, D. N. (1999). Architecture and connections of retrosplenial area 30 in the rhesus monkey (Macaca mulatta). *European Journal of Neuroscience*, *11*, 2506-2518. doi: 10.1046/j.1460-9568.1999.00672.x

Moscovitch, M. (1992). Memory and working-with-memory- A component process model based on modules and central systems. *Journal of Cognitive Neuroscience*, *4*, 257-267. doi: 10.1162/jocn.1992.4.3.257

Murray, E. A., & Bussey, T. J. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Science*, *3*, 142-151.

Murray, E. A., Bussey, T. J., & Saksida, L. M. (2007). Visual Perception and Memory: A New View of Medial Temporal Lobe Function in Primates and Rodents. *Annual Review of Neuroscience*, *30*, 99-122. doi: 10.1146/annurev.neuro.29.051605.113046

Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? *Consciousness and Cognition*, *14*, 390-425. doi: 10.1016/j.concog.2004.10.003

Norman, K. A. (2010). How hippocampus and cortex contribute to recognition memory: revisiting the complementary learning systems model. *Hippocampus*, *20*, 1217-1227. doi: 10.1002/hipo.20855

Norman, K. A., & O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychological Review*, *110*, 611-646. doi: 10.1037/0033-295X.110.4.611

O'Neil, E. B., Cate, A. D., & Köhler, S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *Journal of Neuroscience*, *29*, 8329-8334. doi: 10.1523/JNEUROSCI.0374-09.2009

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *360*, 781. doi: 10.1098/rstb.2005.1631

Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience*, *11*, 1011-1036. doi: 10.1046/j.1460-9568.1999.00518.x

Petrides, M., & Pandya, D. N. (2006). Efferent association pathways originating in the caudal prefrontal cortex in the macaque monkey. *Journal of Computational Neurology*, *498*, 227-251. doi: 10.1002/cne.21048

Protzner, A. B., & McIntosh, A. R. (2006). Testing effective connectivity changes with Structural Equation Modeling: What does a bad model tell us? *Human Brain Mapping*, *27*, 935-947. doi: 10.1002/hbm.20233

Protzner, A. B., & McIntosh, A. R. (2008). Modulation of Ventral Prefrontal Cortex Functional Connections Reflects the Interplay of Cognitive Processes and Stimulus Characteristics. *Cerebral Cortex*, *19*, 1042-1054. doi: 10.1093/cercor/bhn146

Pruessner, J. C., Köhler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani. N., Collins, D. L., & Evans, A. C. (2002). Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. *Cerebral Cortex*, *12*, 1342-1353. doi: 10.1093/cercor/12.12.1342

Ranganath, C., Heller, A., Cohen, M. X., Brozinsky, C. J., & Rissman, J. (2005). Functional connectivity with the hippocampus during successful memory formation. *Hippocampus*, *15*, 997-1005. doi: 10.1002/hipo.20141

Rugg, M. D., Fletcher, P. C., Chua, P. M., & Dolan, R. J. (1999). The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. *Neuroimage*, *10*, 520-529.

Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2007). Impairment and facilitation of transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. *Cerbral Cortex*, *17*, 108-115. doi: 10.1093/cercor/bhj128

Shrager, Y., Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Intact visual perception in memory-impaired patients with medial temporal lobe lesions. *Journal of Neuroscience*, *26*, 2235-2240. doi: 10.1523/JNEUROSCI.4792-05.2006

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience*, *4*, 637-648. doi: 10.1038/nrn1178

Skinner, E. I., & Fernandes, M. A. (2007). Neural correlates of recollection and familiarity: a review of neuroimaging and patient data. *Neuropsychologia*, *45*, 2163-2179. doi: 10.1016/j.neuropsychologia.2007.03.007

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*. 279-306. doi: 10.1146/annurev.neuro.27.070203.144130

Stevens, W. D., Hasher, L., Chiew, K. S., & Grady, C. L. (2008). A neural mechanism underlying memory failure in older adults. *Journal of Neuroscience*, *28*, 12820-12824. doi: 10.1523/JNEUROSCI.2622-08.2008

Suzuki, W. A., & Amaral, D. G. (1994). Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *Journal of Computational Neurology*, *350*, 497-533. doi: 10.1002/cne.903500402

Suzuki, W. A. (2009). Perception and the Medial Temporal Lobe: Evaluating the Current Evidence. *Neuron*, *61*, 657-666. doi: 10.1016/j.neuron.2009.02.008

Suzuki, W. A. (2010). Untangling memory from perception in the medial temporal lobe. *Trends in Cognitive Science*, *14*, 195-200. doi: 10.1016/j.tics.2010.02.002

Vann, S. D., Aggleton, J. P., & Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience*, *10*, 792-802. doi: 10.1038/nrn2733

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cognitive Science*, *9*, 445-453. doi: 10.1016/j.tics.2005.07.001

Chapter 5

5 General Discussion

Mike Tarr recounts that his colleague Robert G. Crowder was fond of saying that "Memory is perception" (Pameri and Tarr, 2008). Indeed, it is challenging to think about one purely isolated from the other. Human experience is an emergent property of information processing in the brain, but at the same time, ongoing experience actively shapes how the brain processes information. The overarching goal of the projects that comprise my thesis was to probe the functional role of PrC in recognition memory and visual perception. Specifically, I examined the hypothesis that contributions of PrC, a region classically viewed as dedicated to declarative memory processing, might be better captured by appealing to the nature of the representations it supports rather than to broad distinctions between memory and visual perception.

In Chapter 2, I revealed that PrC involvement reflected task demands that emphasized individuation of faces, consistent with a role of this region in the development of highly integrated stimulus representations. Activity in PrC was significantly reduced when stimuli could be discriminated based on a simple perceptual feature. Probing the impact of a secondary manipulation, stimulus inversion, hinted at an effect specific to the memory condition. Multivariate PLS analyses revealed that PrC, the FFA, and the Amy were part of a pattern of regions exhibiting preferential activity for tasks emphasizing stimulus individuation, as well the inversion effect.

In Chapter 3, I provided evidence of resting-state connectivity between face-selective aspects of PrC, the FFA and the AMY. The findings of this resting-state analysis point to a privileged functional relationship among these regions, consistent with task-related co-recruitment as revealed in Chapter 2. These results suggest an interactive mechanism by which PrC may participate in the representation of faces. In addition, FFA-PrC connectivity was linked to the magnitude of the face inversion effect in the recognition memory task from Chapter 2 across subjects. This indicates that functional connectivity between these regions is behaviorally relevant.

In Chapter 4, I provided evidence that distinctions between recognition memory and perceptual discrimination demands can be captured by the pattern of PrC connectivity with the rest of the brain. Connectivity common to memory and visual perception tasks was also uncovered. Further, the strength of unique coupling was related to behavioral performance for the memory task.

Together, these findings indicate that mnemonic demands are not the sole arbiter of PrC involvement. Instead, they highlight a role of PrC in the discrimination of faces, perceptual or mnemonic, a role likely facilitated by intrinsic connectivity between PrC and the FFA. They bring to the forefront the importance of connectivity-based approaches in elucidating the role of PrC in memory and visual perception. In this Chapter, I discuss the extent to which my findings support the representational view, before addressing alternate interpretations of the data.

5.1 Findings in Support of a Representational View

The key tenets of the representational view hold that PrC supports representational rather than mnemonic demands, and secondly, that PrC is functionally distinguished from regions more posterior in the ventral visual pathway. Concerning the latter, PrC is thought to be better able to capture the unique co-occurrence of features that define a specific object. In this manner, PrC supports discrimination when stimuli are highly similar, or when they must be maintained over a delay period.

With respect to the first tenet, the comparable PrC involvement in memory and oddity tasks, as demonstrated in Chapter 2, indicates that PrC involvement does not hinge on the introduction of explicit mnemonic demands, consistent with a role of this region in supporting object representations rather than memory per se. Further support for a representational role comes from the findings of Chapter 4, where differential functional connectivity of PrC during recognition memory and perceptual discrimination tasks was revealed. Task-related connectivity provides evidence that goes beyond initial fMRI findings linking PrC involvement to perceptual discrimination demands (Barense et al., 2005; Barense et al., 2010; Barense et al., 2011; Devlin and Price, 2007; Lee et al., 2006; Lee and Rudebeck, 2010; Lee et al., 2008; O'Neil et al., 2009). PrC appears to play a

common role in memory and oddity tasks, tasks designed to have contrasting mnemonic demands. The distinct functional connectivity of PrC during these two task conditions indicates that the neural correlates of object memory may be better captured by patterns of activity across the brain, rather than the presence or absence of PrC activation. Thus, broad distinctions between memory and perception may be reflected at the level of network processing rather than at the level of individual structures. These findings support a more general representational role of PrC in object discrimination tasks.

With respect to the second tenet, several aspects of my findings provide insight into the specific representational demands that engage PrC. The findings of the visual search task in Chapter 2 indicate that response levels in PrC can differ significantly even with the same perceptual input. Rather than reflecting the presence or absence of faces in the experimental display, PrC involvement reflected the extent to which performance on discrimination tasks relied upon the individuation of face stimuli. This finding is consistent with the view that PrC supports object representations that are highly integrated at the feature level. Furthermore, in Chapter 3, I demonstrated functional connectivity between face-selective PrC and the FFA. Classically, FFA is proposed to support the most highly integrated representations of faces. Selective resting-state connectivity between PrC and the FFA, rather than the more posterior OFA for instance, is expected if PrC supports an additional level of feature integration, extending the representational hierarchy of the ventral visual pathway. In addition, sensitivity of PrC to a well established holistic processing manipulation (face inversion) provides some indication that PrC activity can reflect successful integration of features into a bound, object-level representation.

5.2 Challenges to the Representational View

While the findings just reviewed support a representational view, this perspective does not easily accommodate several other findings presented here. In particular, across studies, there are indications that mnemonic demands can create conditions in which PrC activity is tied to behavioral performance. First, modulation of PrC activity by stimulus inversion appeared to impact the memory task but not the perceptual oddity task in Chapter 2. Second, resting-state connectivity between PrC and the FFA, as examined in

Chapter 3, correlated with the magnitude of the behavioral inversion effects for only the memory task. Further investigation of the relationship between PrC-FFA connectivity and the behavioral inversion effect in the perceptual oddity task did not reveal a reliable relationship. Finally, in Chapter 4, behavioral performance was related to the strength of the coupling between task-relevant networks and PrC for recognition memory but not perceptual oddity tasks. These findings may seem puzzling, as PrC activity was not broadly linked to mnemonic functioning. Instead, activity during memory and perceptual oddity tasks was generally comparable. In addition, preferential involvement of PrC in the upright memory condition as compared to the inverted memory condition in Chapter 3 suggests that PrC is not uniformly recruited by tasks with imposed mnemonic demands. A possible account of these findings relates to additional factors in the oddity task that may have de-coupled behavioral performance from measures of PrC activity. It may have been possible, in a small subset of oddity trials, to discriminate stimuli based upon a simple feature (such as luminance). If this were the case, it would weaken the relationship between a neural correlate of feature integration and behavioral accuracy on the oddity task. Perceptible changes in luminance across the target and foil images would be less likely to support memory retrieval, however, given the sheer number of face images encountered between study and test. The larger behavioral impact of inversion for upright memory as compared to the oddity task (Chapter 2) may reflect this task difference. Further research will be required in order to shed light on this issue.

My findings raise two broad issues that will be discussed in the remaining sections of my thesis. First, what is the unique role of PrC in face perception? Similar to others (Anzellotti et al., 2013; Nestor et al., 2011), PrC contributions to the discrimination of faces in the current study appear somewhat redundant with other regions, in particular the amygdala and the FFA. While there are some suggestions of a unique contribution of the anterior face patch in the macaque (Freiwald and Tsao, 2010), my findings do not directly address this issue. Co-activation of PrC, AMY and FFA in my experimental chapters can be interpreted as highlighting a common role of these regions with respect to supporting mnemonic and perceptual discrimination of faces. Indeed, my findings for the most part highlight commonalities rather than distinctions with respect to these regions, the FFA and PrC in particular. While this serves to

highlight the key thesis of the representational view, that MTL and VVS regions are not as distinct as the standard model of MTL functioning holds, my findings fall short of providing conclusive evidence of the *unique* nature of contributions of PrC to face representations. The following section will discuss some recent evidence highlighting distinctions between PrC and VVS regions, interpreted from the perspective of the representational view, specifically by appealing to a role of PrC in the resolution of feature interference.

A second issue is that PrC involvement in tasks with high representational demands need not reflect representation of item information. The use of multi-item displays was extremely helpful in providing a discrimination task with minimal declarative memory demands. However, a drawback of this approach is that it precluded me from linking PrC activity to a specific item representation. While, as reviewed in the introduction, convergent evidence from computational modeling, as well as non-human primate, human patient and neuroimaging evidence points to such a role, admittedly, the specific information processing contributions of PrC are still not fully understood. Following discussion below on the role of interference, I next turn to a discussion of alternative interpretations of PrC involvement in perceptual tasks, in particular related to incidental encoding of stimuli, working memory and long-term memory demands.

5.3 PrC Contributions to the Resolution of Feature Interference

While I attempted to maximize feature ambiguity through the use of morphed face stimuli, in the translation from a visual to a neural code, visually-based assumptions about feature overlap may not map directly on to the neural representations. The precise determination of what actually constitutes feature ambiguity in anterior regions of the ventral visual pathway presents a major research challenge to neuroscience. Feature ambiguity is typically related to high between-item interference arising from the visual similarity of items that comprise the oddball display (e.g. the oddity displays in Chapters 2 and 4). Feature ambiguity can also result from stimulus exposure history. Stimulus exposure history provides a context that guides the level of representations relevant for object discrimination. For instance, when viewing a series of cars, you may naturally

begin to attend to more specific perceptual details than if you were viewing a car image in the context of a wide variety of objects. From a representational view, this recent stimulus history can create conditions of high feature overlap, requiring more integrated representations for successful item discrimination. Recent studies have attempted to probe the representational role of PrC by maximizing this across-trial item interference by presenting a large number of trials of highly similar items. This method has recently been used to shed light on the relationship between PrC and earlier ventral visual pathway regions.

Mundy and colleagues (2013) revealed increased PrC activity during presentation of highly similar faces and objects, whereas a similar pattern was found for scenes in the posterior hippocampus. Classic category-selective areas, namely a face selective region in the fusiform gyrus (FFA), a place selective region on the border of the parahippocampal and lingual gyrus (PPA), and an object selective region (LOC) presented a different pattern of response. Specifically, these regions exhibited increased activity when stimulus exposure history resulted in conditions of low feature overlap as compared to conditions of high feature overlap. Again, this effect was specific to the preferred stimulus class of the respective cortex. This study suggests that feature interference can accumulate over trials, and that PrC and more posterior category-selective regions in the ventral visual pathway differ in response to the buildup of this feature interference. Also of interest is that VVS effects appeared constrained to category selective regions, indicating that the effects of feature interference appear to be domain specific.

The findings of Mundy et al., (2013) are partially consistent with those of another imaging study that examined the effects of feature overlap on PrC. My master's thesis (O'Neil et al., 2009) probed accuracy-related activity in FFA for easy and more difficult face oddity tasks. Activity in FFA was modulated by accuracy in the easy oddity condition, but not in the more difficult oddity condition. In contrast, PrC exhibited modulation by accuracy for both levels of difficulty. This finding is consistent with a reduced representational capacity of more posterior ventral visual pathway regions. Together, these studies indicate that conditions of high feature overlap can result in a increased reliance on PrC in the representation of objects when the representational

capacity of earlier ventral visual areas, even regions that are thought to have some specialization for a particular stimulus class, are insufficient for discrimination.

Additional evidence for a specialized role of PrC in resolving temporal accumulation of feature interference comes from a study by Barense et al. (2012). In this study, the effects of trial history were examined directly in patients with MTL damage. Subjects made same/different judgments on pairs of images. Critical probe trials were interleaved with trials designed to create conditions of high or low feature interference. In the high feature interference condition, probe and filler trials were composed of a common set of features, while filler stimuli in the low feature interference condition did not share features with the critical probe trials. Patients with MTL damage performed as well as control subjects when intervening trials were of low feature overlap, but were impaired when intervening trials had high feature overlap.

These studies, while not directly addressing the hard problem of quantifying the transformations in the representational code as information is propagated throughout the ventral visual pathway, do support the notion that PrC contributes to the resolution of feature interference in a way that distinguishes it from more posterior ventral visual pathway regions. In particular, it appears that PrC and more posterior regions are differentially influenced by feature interference.

PrC involvement in between-trial and between-item (i.e., within-trial) discrimination blurs the lines of working memory, i.e., maintenance, and perceptual demands, but point to a common role of PrC across tasks in the resolution of feature interference. Further investigation of how between- and within-trial feature interference manipulations interact would be fruitful in determining the contributions of PrC in the resolution of interference, and the timescales of interaction between PrC and VVS given the recurrent nature of VVS - PrC projections (Kravitz et al., 2013). An interesting possibility is that the recurrent nature of PrC processing may lead to patterns of activity in VVS regions that are less stable and more dynamic under conditions in which PRC is active, reflecting iterative tuning of lower level inputs to maximize the discriminability of PrC-based representations. Techniques with more precise temporal resolution than those

employed in the current set of studies, in combination with analysis techniques which can assess the representational content of regions, would be necessary in order to effectively test this prediction.

5.4 Alternative Interpretations: Incidental Encoding

I interpret the findings of my three core thesis chapters as supporting a representional view of PrC functioning. However, alternative interpretations also require consideration. Rather than reflecting contributions to perception, PrC involvement during oddity discrimination tasks may relate to the incidental encoding of the stimuli, i.e., memory formation. This interpretation would allow PrC involvement in perceptual discrimination tasks to be reconciled with the standard model of MTL functioning, as it would point to a mnemonic rather than perceptual contribution of MTL stuctures. Several lines of evidence speak against such an interpretation. If PrC activity during perceptual discrimination tasks reflects stimulus encoding, this activity should differentiate conditions of high and low encoding demands. More specifically, PrC should exhibit increased activity for novel stimuli as compared to familiar due to increased encoding demands. Instead, Barense et al. (2011a) revealed preferential responses to known faces and objects as compared to unfamiliar. In addition, PrC activity during the discrimination of known or unknown items was not related to subsequent recognition of items in a memory test at the end of the experimental session. I previously reported similar findings in a follow-up behavioural study of my Master's thesis data (O'Neil et al., 2009, supplemental materials). In this study, we examined subsequent memory for correctly versus incorrectly identifed oddity items. No differences in accuracy were found for these items. It is difficult to account for these findings from an encoding-demands perspective of PrC involvement. I do not claim that encoding and perception are entirely distinct, rather I highlight that PrC activity is not strictly related to encoding demands in perceptual discrimination tasks. This suggests that processing related to encoding cannot exclusively account for PrC involvement in tasks with minimal memory demands.

5.5 Alternative Interpretations: Long Term and Working Memory Contributions

The current findings provide evidence for PrC involvement in long-term memory as well as perceptual discrimination tasks. Might MTL structures also support working memory? The neuroanatomical substrates of WM and LTM have been classically viewed as distinct (Atkinson and Shiffrin, 1980; Milner, 1972; Squire, 2009). Damage to MTL structures impairs long-term memory for words and digit lists, but working memory for these stimuli is preserved (Baddeley and Warrington, 1970; Cave and Squire, 1992). This dissociation has contributed to the prevailing view that MTL functioning supports long-term declarative memory processing rather than working memory (or perception). This distinction appears difficult to square with a representational view of PrC functioning, which predicts PrC involvement whenever highly integrated object representations are required to support resolution of feature ambiguity. Notably, however, evidence that supports this classic distinction comes mainly from demonstrations of intact working memory in amnesiacs for information that can be verbally rehearsed (such as digits and words).

Recent findings indicate that patients with MTL damage can exhibit deficits on working memory tasks (see Ranganath and Blumenfeld, 2005 for review). These deficits appear related to representational demands; patients with MTL damage exhibit WM impairments if the information to be maintained relies on relational information, or on the maintenance of novel information that is difficult to verbalize (e.g., Olson et al., 2006; Rose et al., 2012; Warren et al., 2010). These and other findings have led some researchers to suggest that working memory and activated long-term memory may have a common neural substrate (Jonides et al., 2005; Postle, 2006; Ranganath and Blumenfeld, 2005; Ranganath and D'Esposito, 2001). In fact, a recent behavioral finding indicates that perceptual aspects of WM and LTM representations have similar fidelity (Brady et al., 2013), suggestive of the notion that WM and LTM may share a common, or at least similar representational code.

Important evidence supporting a role of the MTL in WM comes from a recent study examining PrC involvement during the active maintenance of face images. Olsen et

al. (2009) examined BOLD response during a working memory task for unfamiliar faces, a stimulus class that is difficult to verbally rehearse. Critically, MTL activity was present during four or 30 s delay periods, consistent with these regions supporting active maintenance of information over short delays. Moreover, MTL delay-period activity was linked to subsequent memory of the items immediately following the delay. Thus, it appears that contributions of MTL structures during the delay-period are behaviorally relevant to WM performance. No relationship to subsequent memory was revealed in the fusiform. Similarly, findings from MTL damaged patients have revealed impairments in WM for faces after 7 s, but not 1 s delays (Nicols et al., 2006). Both of these findings are consistent with MTL contributions to the active maintenance of face information over short (longer than one second) delay periods. This role is consistent with PrC supporting representations that are robust to interference from ongoing perceptual experience over a delay.

It might be the case that contributions of PrC to perceptual discrimination tasks also reflect the presence of working-memory demands. Typically, PrC activity during perceptual discrimination tasks is demonstrated using oddity paradigms where subjects view arrays of multiple visually complex stimuli. To determine the oddball item, subjects must compare images, maintaining representations online when fixating between items. The nature of these demands raises the possibility that PrC involvement in these tasks may relate to the maintenance of stimuli information, rather than perceptual processing per se.

One important distinction with respect to the role of PrC in the maintenance of items during an explicit delay period as compared to the maintenance of representation over much briefer intervals (i.e., between fixations in an oddity display) relates to subsequent memory effects previously described. PrC activity over explicit delays has been tied to subsequent memory (Olsen et al., 2009), whereas PrC activity related to oddity discrimination has not (Barense et al., 2011a; O'Neil et al., 2009). This suggests that PrC contributions during perceptual discriminations differ to some extent from those related to maintenance over unfilled longer delays. This pattern of results indicates that the relationship between PrC activity and working memory demands is not

straightforward. More generally, distinguishing working memory demands related to the ongoing processing of a currently viewed stimuli and the perception of the stimuli is challenging, if not impossible. Ultimately, distinguishing between WM and perception is likely a fruitless endeavor, especially given that contributions of PrC to both WM and perceptual tasks could be predicted by the representational view. MTL involvement in WM tasks is consistent with the representational view, as it challenges the standard view that this region is dedicated to long-term memory processing.

Links between working and long-term memory, however, raise broader issues surrounding potential mnemonic demands associated with perceptual tasks. While a common MTL substrate supporting long-term and working memory runs counter to the standard model of MTL functioning, some researchers have raised the possibility that MTL contributions to WM tasks reflect conditions where the capacity of WM has been exceeded (Jeneson and Squire, 2011). Squire and colleagues (Jeneson et al., 2010; Shrager et al., 2008) have been at the forefront of raising this potential issue. They make the distinction between 'subspan' and 'supraspan' maintenance demands. Under supraspan maintenance demands, the amount of information being maintained exceeds working memory capacity, relying on an MTL-based long-term memory mechanism to aid in discrimination tasks. These authors have shown that when working memory capacity is exceeded, patients with MTL damage are impaired even under brief retention intervals (Jeneson and Squire, 2011).

Taken to the extreme, it is clear that even when stimuli are simultaneously present in a display, discrimination tasks can be designed that almost certainly rely on LTM representations. Using extremely large stimulus arrays (e.g. >70 items), Warren et al., (2011) revealed impairments in MTL-patients on a match-to-sample task, despite continuous presentation of the target in the middle of the array (Warren et al., 2011). This finding suggests that patients with MTL damage may have intact visual perception, but difficulty actively maintaining an online representation for extended durations (~20 - 60 s). Delay-dependent deficits in object discrimination are a hallmark of PrC lesions, but as reviewed in Chapter 1, and in light of the findings of the three chapters presented here, an imposed delay period does not appear to be a critical determinant of PrC involvement.

The results of Warren et al. (2010), however, indicate that the absence of an explicit delay period may not preclude the use of a long-term memory mechanism.

LTM may also support the discrimination of smaller object arrays. Barense et al., (2007) tested patients on a seven-item oddity task (3 distinct item pairs, and an odd item out), with stimuli designed to have distinct appendages. Patients with MTL damage were impaired on difficult, but not easy oddity discriminations. Of potential concern, with respect to potential LTM contributions to performance on this task, were the error patterns of the control participants. The level of difficulty at which control participants began to commit oddity discrimination errors was identical to that at which patient performance exhibited significant discrimination deficits in comparison to controls. Jeneson et al. (2011) suggests that the tendency of controls to begin making discrimination errors when difficulty is increased provides an indication that working memory demands have been exceeded, increasing reliance on a more fallible LTM representation. From this perspective, discrimination deficits on the oddity task for patients with MTL damage reflect an inability to recruit a long-term memory mechanism, not impairments in the representation of the items. The large number of items in the display (seven), the construction of stimuli with distinct and verbalizable features, and demands related to maintenance of stimulus pair relationships in order to identify the oddball, does leave open the possibility that the task employed by Barense et al. (2007) could benefit from a LTM encoding strategy.

These findings raise important questions with respect to WM capacity and PrC involvement in discrimination tasks. Specifically, it is important to rule out potential WM capacity limitations as an explanation of PrC involvement in discrimination tasks. Of concern is the possibility that PrC involvement hinges on processing demands unique to multi-item displays, which may exceed the capacity of WM, engaging LTM mechanism in order to support discrimination performance. Some insight into this issue can be gained by considering studies that have investigated PrC involvement in object processing using single item displays. This has been explored in MTL-lesioned patients and controls in a possible/impossible object judgment task (Lee et al., 2010). Participants judged individual presentations of 3D wireframe object drawings specially designed such that

some represented coherent objects that could exist in the real world, and some designed to possess violations of 3D structure. Assessment of coherence required the consideration of how object features combined to form the edges and surfaces of the object, a process proposed by the Lee et al. as relying on the integration of object features. Deficits were uncovered in patients with MTL damage as compared to patients with selective hippocampal damage or age-matched controls using single item displays. This finding suggests that WM demands linked to multiple item representations are not responsible for discrimination deficits in MTL-damaged patients. In a somewhat related study, Staresina et al. (2010) examined MTL BOLD response in healthy individuals during viewing of common objects presented with three levels of fragmentation (e.g., presentation of an object after it has been divided into quarters and rearranged). Despite fragmentation being apparently linked to representational demands, level of fragmentation was not found to reflect PrC activity. What accounts for these divergent findings? One critical difference between these studies is that unlike the stimuli used by Lee et al. (2010), object recognition of a quartered image does not require the integration of item features, due to the low feature overlap (i.e., low between-trial similarity) of the stimuli. In other words, unlike impossible objects which required assessment of the full object in order to determine structural plausibility, identification of an a image (e.g., an avocado) can be done based upon the recognition of ¼ of the image, without demanding active integration of the four quadrants into a coherent percept. This pattern of findings, then, is not inconsistent with the representational view. Rather, like the results of the visual search task in Chapter 2, these findings indicate that PrC is not recruited whenever individual complex stimuli are assessed, but instead is active when discrimination requires the integration of object features.

While I cannot rule out the possibility that oddity displays may require the maintenance of representations that exceed the capacity of working memory, several pieces of evidence speak against this interpretation. Unlike the task of Barense et al. (2007) or Warren et al. (2011), morph displays were limited to three items, and designed to minimize the likelihood that verbalizable stimulus features were tracked in order to determine the oddball. Second, the introduction of explicit long-term declarative memory demands failed to increase PrC involvement in the recognition memory as compared to

the oddity task. This suggests, at minimum, that PrC involvement is not directly yoked to the degree of declarative memory demands. Third, capacity estimates of face WM (following a 4 s encoding duration, shorter than the 5 s exposures of oddity trials in Chapters 2 and 4), has been shown to exceed two items, even when stimuli are inverted (Curby and Gauthier, 2007). This suggests that oddity triplets may be within WM capacity. Fourth, if visual perception of three faces does exceed the capacity of working memory, it would be expected that MTL-damaged patients would have catastrophic impairments when interacting in their immediate perceptual environment, which far outstrips the content of oddity displays with respect to richness and complexity. Fifth, in addition to evidence pointing to a role of PrC in the discrimination of individual stimuli (e.g., Lee et al., 2010), or during passive viewing tasks that do not require explicit maintenance of items (e.g., Mundy et al., 2012; Rossion et al., 2012), recent work has expanded the role of PrC to figure-ground discrimination of simple displays of adjacent black and white regions separated by a border (Barense et al., 2011b; Peterson et al., 2012). These displays require integration of features for successful task performance, but at face value appear to possess substantially reduced stimulus complexity as compared to stimuli typically employed to examine PrC functioning. It seems difficult to argue such simple displays could tax WM beyond its capacity. Finally, recruitment of a long-term memory mechanism would be expected to relate to incidental encoding, however as reviewed in the section above, this is not the case.

5.6 Future Directions

The results presented in the experimental chapters presented here highlight several future avenues of research that would help to address some key issues that remain regarding PrC contributions to representational processing.

First, convergent evidence of the role of PrC in perceptual oddity, recognition memory, and visual search tasks from a population with impaired PrC connectivity would greatly strengthen the conclusions of the findings presented here. One such population is congenital prosopagnosics, who exhibit reduced integrity of the inferior longitudinal fasciculus, the white matter tract that links PrC to FFA (Thomas et al., 2009). I would predict that these patients would be impaired on recognition memory and perceptual

oddity tasks, while performance for the visual search task would be similar to that of controls. I would also predict that deficits in recognition memory and perceptual oddity tasks would relate to the extent of reduced longitudinal fasciculus integrity, consistent with the findings of Thomas (2009).

Second, face-selective response in PrC during the passive viewing localizer scans, as revealed in Chapter 2, raises an important question with respect to active vs. passive individuation of faces. Is the response of PrC to faces the result of obligatory and feed-forward processing that occurs whenever attentional constraints permit assessment of face content? From this perspective, demands of the visual search task disrupted face processing, resulting in reduced FFA activity, and thus reduced inputs to PrC. Alternatively, recruitment of PrC may relate to the active individuation of faces. From this latter perspective, PrC contributions to face processing are the result of a controlled optimization process by which recurrent processing between PrC and more posterior ventral visual regions support the development of maximally distinct object representations. PrC projects to greater portions of TE and TEO (posterior visual regions in the monkey that provide the major source of PrC inputs) than it receives inputs from, providing an opportunity to greatly influence the nature of processing in more posterior regions (Lavenex et al., 2002). In addition, PrC projections to V1 (Clavagnier et al., 2004), or multi-synaptic connectivity with V4 (Ninomiya et al., 2012), could facilitate the top-down shaping of sensory inputs. This view could account for face-selective response of PrC during the localizer task by appealing to a natural tendency to process highly engaging stimuli such as faces. The current experimental designs cannot address this distinction directly. Future approaches should aim to disrupt potential feedback processes through the use of brief item displays in conjunction with forward image masking to introduce noise in more posterior ventral visual pathway regions. This approach may shed some light on the extent to which representational processing differs across regions. A recent report highlights largely redundant representational content across regions where face identity could be decoded from BOLD activation (Nestor et al., 2011). A recurrent processing view could account for this redundancy as a by-product of the poor temporal resolution of fMRI. Multi-second TR's would allow for the summing of BOLD signal over many iterations of representation optimization, increasing the homogeneity of

representational content across regions as initially unique information that is the result of localized processing is propagated throughout the system. Disruption of recurrent processing between PrC and more posterior ventral visual regions through the introduction of competing inputs (the mask) may reveal greater distinctions with respect to the specific representational contributions across regions.

Finally, to gain a more thorough understanding of PrC contributions to object representation, a range of stimulus classes, beyond faces, must be assessed. PrC has been linked to the discrimination of non-face objects (Barense et al., 2007; Barense et al., 2012; Barense et al., 2010; Buckley et al., 2001; Devlin and Price, 2007; Lee et al., 2005a; Lee et al., 2005b; Lee and Rudebeck, 2010). Further, recent evidence points to distinct patterns of right PrC response to faces, buildings, and chairs (Martin et al., 2013). These reliable response patterns to distinct object categories may be facilitated by specialized connectivity with object- and scene-selective regions, similar to face-specific connectivity findings revealed in Chapter 2. Investigation of the functional connectivity between PrC and object-selective regions would provide important insights into the broader contributions of PrC functional connectivity to object representation.

Taken together, the experimental findings of each of the three projects presented here highlight reliable patterns of connectivity between PrC and VVS regions. These findings point to a representational role of PrC, and blur the lines between memory and perception. Future work must aim to better delineate the relationship between PRC and ventral visual regions in stimulus classes beyond faces. Further, the actual representational content of PrC is still poorly understood. MVPA approaches in conjunction with single item displays will likely go further in elucidating the informational content of PRC. Finally, the impact of working memory demands warrants further research, in order to address more definitively whether PrC involvement in perception reflects demands that hinge on active maintenance of item representations.

5.7 References

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In the Psychology of Learning and Motivation: II (ed. KW Spense, JT Spence). Academic Press, Oxford.

Anzellotti, S., Fairhall, S. L., Caramazza, A. (2013). Decoding Representations of Face Identity That are Tolerant to Rotation. *Cerebral Cortex*, *23*, 1-8. doi: 10.1093/cercor/bht046

Baddeley, A. D., & Warrington, E. K. (1970). Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behavior*, *9*, 176-189.

Barense, M. D., Bussey, T. J., Lee, A. C. H., Rogers, T. T., Davies, R. R., Saksida, L. M., Murray, E. A., & Graham, K. S. (2005). Functional specialization in the human medial temporal lobe. *The Journal of Neuroscience*, *25*, 10239-10246. doi: 10.1523/JNEUROSCI.2704-05.2005

Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, *45*, 2963-2974. doi: 10.1016/j.neuropsychologia.2007.05.023

Barense, M. D., Groen, I. I.A., Lee, A. C. H., Yeung, L-K., Brady, S. M., Gregori, M., Kapur, N., Bussey, T. J., Saksida, L. M., & Henson, R. N. A. (2012). Intact memory for irrelevant information impairs perception in amnesia. *Neuron*, *75*, 157-167. doi: 0.1016/j.neuron.2012.05.014

Barense, M. D., Henson, R. N. A., & Graham, K. S. (2011). Perception and conception: temporal lobe activity during complex discriminations of familiar and novel faces and objects. *Journal of Cognitive Neuroscience*, *23*, 3052-3067. doi: 10.1162/jocn_a_00010

Barense, M. D., Henson, R. N. A., Lee, A. C. H., & Graham, K.S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*, 389-401. doi: 10.1002/hipo.20641

Barense, M. D., Ngo, J. K. W., Hung, L. H. T., & Peterson, M. A. (2011). Interactions of memory and perception in amnesia: The figure-ground perspective. Cerebral Cortex, 22, 2680-2691. doi: 10.1093/cercor/bhr347

Brady, T. F., Konkle, T., Gill, J., Oliva, A., & Alvarez, G. A. (2013). Visual long-term memory has the same limit on fidelity as visual working memory. *Psychological Science*, *24*, 981-990. doi: 10.1177/0956797612465439

Buckley, M. J., Booth, M. C., Rolls, E. T., & Gaffan, D. (2001). Selective perceptual impairments after perirhinal cortex ablation. *The Journal of Neuroscience*, *21*, 9824-9836.

Cave, C., & Squire, L. R. (1992). Intact verbal and nonverbal short-term memory following damage to the human hippocampus. *Hippocampus*, *2*, 151-163. doi: 10.1002/hipo.450020207

Clavagnier, S., Falchier, A., & Kennedy, H. (2004). Long-distance feedback projections to area V1: implications for multisensory integration, spatial awareness, and visual consciousness. *Cognitive, Affective & Behavioral Neuroscience*, *4*, 117-126.

Curby K.M., & Gauthier, I. (2007). A visual short-term memory advantage for faces. *Psychonomic Bulletin & Review, 14,* 620-628.

Devlin, J. T., & Price, C. J. (2007). Perirhinal contributions to human visual perception. *Current Biology*, *17*, 1484-1488. doi: 10.1016/j.cub.2007.07.066

Freiwald, W. A., & Tsao, D. Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, *330*, 845-851. doi: 10.1126/science.1194908

Jeneson, A., Mauldin, K. N., & Squire. L. R. (2010). Intact working memory for relational information after medial temporal lobe damage. *The Journal of Neuroscience*, *30*, 13624-13629. doi: 10.1523/JNEUROSCI.2895-10.2010

Jeneson, A., & Squire, L. R. (2011). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory*, *19*, 15-25. doi: 10.1101/lm.024018.111

Jonides, J., Lacey, S., & Nee, D. (2005). Processes of working memory in mind and brain. *Current Directions in Psychological Science*, *14*, 1-5. doi: 10.1111/j.0963-7214.2005.00323.x

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends in Cognitive Sciences*, *17*, 26-49. doi: 10.1016/j.tics.2012.10.011

Lavenex, P., Suzuki, W. A., & Amaral, D. G. (2002). Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *Journal of Computational Neurology*, *447*, 394-420. doi: 10.1002/cne.10243

Lee, A. C. H., Bandelow, S., Schwarzbauer, C., Henson, R. N. A., & Graham, K. S. (2006). Perirhinal cortex activity during visual object discrimination: an event-related fMRI study. *NeuroImage*, *33*, 362-373. doi: 10.1016/j.neuroimage.2006.06.021

Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H., Scahill, V. L., Gaffan, D., Bussey, T. J., Davies, R. R., Kapur, N., Hodges, J. R. and others. (2005). Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, *15*, 782-797. doi: 10.1002/hipo.20101

Lee, A. C. H., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., Hodges, J. R., & Graham, K. S. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*, *43*, 1-11. doi: 6/j.neuropsychologia.2004.07.017

Lee, A. C. H., & Rudebeck, S. R. (2010). Human medial temporal lobe damage can disrupt the perception of single objects. *The Journal of Neuroscience*, *30*, 6588-6594. doi: 10.1523/JNEUROSCI.0116-10.2010

Lee, A. C., Scahill, V. L., & Graham, K. S. (2007). Activating the Medial Temporal Lobe during Oddity Judgment for Faces and Scenes. *Cerebral Cortex*, *18*, 683-696. doi: 10.1093/cercor/bhm104

Martin, C. B., McLean, D. A., O'Neil, E. B., & Köhler, S. (2013). Distinct familiarity-based response patterns for faces and buildings in perirhinal and parahippocampal cortex. *The Journal of Neuroscience*, *33*, 10915-10923. doi: 10.1523/JNEUROSCI.0126-13.2013

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, *19*, 421-446.

Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: Complementary findings from amnesia and fMRI. *The Journal of Neuroscience*, *33*, 10490-10502. doi: 10.1523/JNEUROSCI.2958-12.2013

Mundy, M. E., Downing, P. E., & Graham, K. S. (2012). Extrastriate cortex and medial temporal lobe regions respond differentially to visual feature overlap within preferred stimulus category. *Neuropsychologia*, 50, 3053-3061. doi: 10.1016/j.neuropsychologia.2012.07.006

Nestor, A., Plaut, D. C., & Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 9998-10003. doi: 10.1073/pnas.1102433108

Nicols, E.A., Kao, Y, Verfaellie, M., & Gabrieli, J.D.E. (2006). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvment of the medial temporal lobes. *Hippocampus*, 16, 604-616. doi: 10.1002/hipo.20190

Ninomiya, T., Sawamura, H., Inoue, Ki., & Takada, M. (2012). Multisynaptic Inputs from the Medial Temporal Lobe to V4 in Macaques. *PLoS ONE*, 7, e52115. doi:10.1371/journal.pone.0052115

O'Neil, E. B., Cate, A. D., & Köhler, S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *The Journal of Neuroscience*, *29*, 8329-8334. doi: 10.1523/JNEUROSCI.0374-09.2009

Olsen, R. K., Nichols, E. A., Chen, J., Hunt, J. F., Glover, G. H., Gabrieli, J. D. E., & Wagner, A. D. (2009). Performance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample. *The Journal of Neuroscience*, *29*, 11880-11890. doi: 10.1523/JNEUROSCI.2245-09.2009

Olson, I. R., Moore, K. S., Stark, M., & Chatterjee, A. (2006). Visual working memory is impaired when the medial temporal lobe is damaged. *Journal of Cognitive Neuroscience*, *18*, 1087-1097. doi: 10.1162/jocn.2006.18.7.1087

Palmeri, T. J., & Tarr, S. J. Visual object perception and long-term memory. In Luck SJ, Hollingworth AR, eds. Visual Memory. New York: Oxford University Press, 2008:163-208.

Peterson, M. A., Cacciamani, L., Barense, M. D., & Scalf, P. E. (2012). The perirhinal cortex modulates V2 activity in response to the agreement between part familiarity and configuration familiarity. *Hippocampus*, *22*, 1965-1977. doi: 10.1002/hipo.22065

Postle, B. R. (2006). Working memory as an emergent property of the mind and brain. *Neuroscience*, 139, 23-38. doi: 10.1016/j.neuroscience.2005.06.005

Ranganath, C., & Blumenfeld, R. S. (2005). Doubts about double dissociations between short- and long-term memory. *Trends in Cognitive Sciences*, *9*, 374-380. doi: .1016/j.tics.2005.06.009

Ranganath, C., & D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron*, *31*, 865-873. doi: 10.1016/S0896-6273(01)00411-1

Rose, N. S., Olsen, R. K., Craik, F. I. M., & Rosenbaum, R. S. (2012). Working memory and amnesia: the role of stimulus novelty. *Neuropsychologia*, *50*, 11-18. doi: 10.1016/j.neuropsychologia.2011.10.016

Rossion, B., Hanseeuw, B., & Dricot, L. (2012). Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. *Brain and Cognition, 79*, 138-157. doi: 10.1016/j.bandc.2012.01.001

Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Activity in both hippocampus and perirhinal cortex predicts the memory strength of subsequently remembered information. *Neuron*, *59*, 547-553. doi: 10.1016/j.neuron.2008.07.022

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron*, *61*, 6-9. doi: 10.1016/j.neuron.2008.12.023

Staresina, B. P., & Davachi, L. (2010). Object unitization and associative memory formation are supported by distinct brain regions. *The Journal of Neuroscience*, *30*, 9890-9897. doi: 10.1523/JNEUROSCI.0826-10.2010

Thomas, C., Avidan, G., Humphreys, K., Jung, K. J., Gao, F., & Behrmann, M. (2009). Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nature Neuroscience*, *12*, 29-31. doi: 10.1038/nn.2224

Warren, D. E., Duff, M. C., Tranel, D., & Cohen, N. J. (2010). Medial temporal lobe damage impairs representation of simple stimuli. *Frontiers in Human Neuroscience*, 4, 1-9. doi: 10.3389/fnhum.2010.00035

Warren, D. E., Duff, M. C., Tranel, D., & Cohen, N. J. (2011). Observing degradation of visual representations over short intervals when medial temporal lobe is damaged. *Journal of Cognitive Neuroscience*, *23*, 3862-3873. doi: 10.1162/jocn_a_00089

Appendix A

Office of Research Ethics

The University of Western Ontario

Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. S. Kohler

Review Number: 08182E **Revision Number:** 1

Review Date: October 31, 2008 **Review Level:** Expedited

Protocol Title: The neural substrates of episodic long-term memory for visually apprehended information.

Department and Institution: Psychology, University of Western Ontario

Sponsor:

Ethics Approval Date: October 31, 2008 **Expiry Date:** July 31, 2010

Documents Reviewed and Approved: Administrative changes. Revised Letter of Information and Consent (September 2008).

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland	☐ Elizabeth Wambolt	☑ Grace Kelly	☐ Denise Grafton

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. S. Kohler
Review Level: Expedited
Review Number: 08182E
Revision Number: 3
Review Date: April 28, 2010
Approved Local # of Participants: 250
Protocol Title: The neural substrates of episodic long-term memory for visually apprehended information.
Department and Institution: Psychology, University of Western Ontario
Sponsor:
Ethics Approval Date: April 28, 2010
Expiry Date: July 31, 2013
Documents Reviewed and Approved: Revised Study End Date
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland	☐ Elizabeth Wambolt	☐ Grace Kelly	☑ Denise Grafton

This is an official document. Please retain the original in your files.

cc: ORE File

Curriculum Vitae

Post-secondary Education and Degrees:

2001-2005 B.A. (Hons.)
The University of Western Ontario

2006-2008 M.Sc.
The University of Western Ontario

2008-Present Ph.D Candidate
The University of Western Ontario

Honors and Awards:

Donald O. Hebb Award, CSBBCS
2008

Best Master's Thesis
Graduate Program in Neuroscience - UWO
2008

OGSST
2009-2010

NSERC Canada Graduate Scholarship - Doctoral
2010-2012

Publications:

Martin, C.B., McLean, D.A., **O'Neil, E.**, & Köhler, S. Distinct familiarity-based response patterns for faces and buildings in perirhinal and parahippocampal cortex. The Journal of Neuroscience, 33(26), 10915–10923.

O'Neil, E., Barkley, V.D., & Köhler, S. (2013) Representational demands modulate involvement of perirhinal cortex in face processing. *Hippocampus*. *23*(7), 592-605.

O'Neil, E., Protzner, A., McCormick, C., McLean, DA., Poppenk, J., Cate, A., & Köhler, S. (2012). Distinct patterns of functional and effective connectivity between perirhinal cortex and other cortical regions in recognition memory and perceptual discrimination. *Cerebral Cortex*. *22*(1), 74–85.

(co-first author) Bowles, B.*, **O'Neil, E.***, Mirsattari, S., Poppenk, J., & Köhler, S. (2011). Preserved hippocampal novelty responses following anterior temporal-lobe resection that impairs familiarity but spares recollection. *Hippocampus*, *21*(8), 847–854.

O'Neil, E., Cate, A., Köhler, S. (2009). Perirhinal Cortex Contributes to Accuracy in Recognition Memory and Perceptual Discriminations. *The Journal of Neuroscience, 29*(26), 8329-8334.